### **PCT**

# WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



# INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6:

G01N 33/50, C12Q 1/48, 1/25

A3

(11) International Publication Number: WO 98/45704

(43) International Publication Date: 15 October 1998 (15.10.98)

(21) International Application Number: PCT/DK98/00145

(22) International Filing Date: 7 April 1998 (07.04.98)

(30) Priority Data:

0392/97 7 April 1997 (07.04.97)

DK

(71) Applicant (for all designated States except US): NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsvaerd (DK).

(72) Inventors; and

(75) Inventors/Applicants (for US only): THASTRUP, Ole [DK/DK]; Birkevej 37, DK-3460 Birkerød (DK). PETERSEN BJØRN, Sara [DK/DK]; Klampenborgvej 102, DK-2800 Lyngby (DK). TULLIN, Søren [DK/DK]; Karl Gjellerups Alle 18, DK-2860 Søborg (DK). KASPER, Almholt [DK/DK]; Eigilsgade 32, 4. tv, DK-2300 København S (DK). SCUDDER, Kurt [US/DK]; Lavendelhaven 70, DK-2830 Virum (DK).

(74) Common Representative: NOVO NORDISK A/S; attn. Lars Kellberg, Novo Allé, DK-2880 Bagsværd (DK). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
22 April 1999 (22.04.99)

(54) Title: A METHOD FOR EXTRACTING QUANTITATIVE INFORMATION RELATING TO AN INFLUENCE ON A CELLULAR RESPONSE

#### (57) Abstract

Cells are genetically modified to expresss a luminophore, e.g., a modified (F64L, S65T, Y66H) Green Fluorescent Protein (GFP, EGFP) coupled to a component of an intracellular signalling pathway such as a transcription factor, a cGMP- or cAMP-dependent protein kinase, a cyclin-, calmodulin- or phospholipid-dependent or mitogen-activated serine/threonin protein kinase, a tyrosine protein kinase, or a protein phosphatase (e.g. PKA, PKC, Erk, Smad, VASP, actin, p38, Jnk1, PKG, IkappaB, CDK2, Grk5, Zap70, p85, protein-tyrosine phosphatase 1C, Stat5, NFAT, NFkappaB, RhoA, PKB). An influence modulates the intracellular signalling pathway in such a way that the luminophore is being redistributed or translocated with the component in living cells in a manner experimentally determined to be correlated to the degree of the influence. Measurement of redistribution is performed by recording of light intensity, fluorescence lifetime, polarization, wavelength shift, resonance energy transfer, or other properties by an apparatus consisting of e.g. a fluorescence microscope and a CCD camera. Data stored as digital images are processed to numbers representing the degree of redistribution. The method can be used as a screening program for identifying a compound that modulates a component and is capable of treating a disease related to the function of the component.

## FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
ΑŪ	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	ŲA	Ukraine
BR	Brazil	ΠL	Israel	MR	Manritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of Americ
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	zw	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
cz	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	. Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Int. Itional Application No PCT/DK 98/00145

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 G01N33/50 C120 C1201/48 C1201/25 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) GO1N C12Q C12N C07K IPC 6 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. X WO 97 11094 A (NOVONORDISK AS ;THASTRUP 1-27, OLE (DK); TULLIN SOEREN (DK); POULSEN LAR) 30-40, 27 March 1997 44-60, 64-82,88 see the whole document Υ see claims 28,29, 41,61-63 X WO 91 01305 A (UNIV WALES MEDICINE) 1-277 February 1991 30 - 40, 42-60, 64-84. 87,88 see page 4, line 15 - line 20 Υ 28,29, see claims 41,61-63 see examples 1-10 | x | Further documents are listed in the continuation of box C. Х Patent family members are listed in annex. Special categories of cited documents : T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance invention "E" earlier document but published on or after the International X° document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) involve an inventive step when the document is taken alone Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents such combination being obvious to a person skilled "O" document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed n the art in sament member of the same patent family Date of the actual completion of the international search Clare of mailing of the international search report **25**. 02. 1999 19 January 1999 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentiaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 Hoekstra, S

9

Int ational Application No PCT/DK 98/00145

	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	I Colonia de la
Category 3	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 07463 A (UNIV COLUMBIA ;WOODS HOLE OCEANOGRAPHIC INST (US); CHALFIE MARTIN) 16 March 1995 cited in the application	1-27, 30-40, 42-60, 64-84, 87,88
Y	see claim 26 see the whole document	28,29, 41,61-63
Υ	WO 96 23898 A (NOVONORDISK AS ;THASTRUP OLE (DK); TULLIN SOEREN (DK); POULSEN LAR) 8 August 1996	28,29, 41,61-63
X	see the whole document see page 8-17	42,43, 46,47
X	WO 96 03649 A (UNIV NORTH CAROLINA) 8 February 1996 see page 49; example 6.10	45
Ρ,Χ	WO 97 20931 A (US HEALTH ;HTUN HAN (US); HAGER GORDON L (US)) 12 June 1997 see claims 41-58	40,44
Ρ,Χ	WO 97 30074 A (CYTOGEN CORP ;UNIV NORTH CAROLINA (US)) 21 August 1997 see page 57	44
Р,Х	WO 98 02571 A (TSIEN ROGER Y ;CUBITT ANDREW B (US); UNIV CALIFORNIA (US)) 22 January 1998	1-27, 30-40, 42-50, 52-54, 57-60, 64-82,88
	see claims	
E	WO 98 30715 A (ISACOFF EHUD Y ;SIEGAL MICAH S (US); UNIV CALIFORNIA (US); CALIFOR) 16 July 1998 see the whole document	1-84,87, 88
	-/	

Int ational Application No PCT/DK 98/00145

	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category 1	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	SAKAI, N. ET AL.: "Direct visualization of the translocation of the gamma subspecies of protein kinase c in living cells using fusion proteins with green fluorescent protein."  THE JOURNAL OF CELL BIOLOGY, vol. 139, no. 6, 15 December 1997, pages 1465-1476, XP002078902 see the whole document	1-43,46, 47,49, 53-57, 59-82,88
O,X	& Direct visualization of the translocation of the gamma subspecies of protein kinase c in living cells using fusion proteins with green fluorescent protein. Meeting held at 22-23.03.97 cited in the application see abstract	
X	SCHMIDT, D.J. ET AL.: "Dynamic analysis of alpha-PKC-GFP chimera translocation events in smooth muscle with ultra-high speed 3D fluorescence microscopy" FASEB JOURNAL, vol. 11, no. 3, 28 February 1997, page A505 XP002077257 cited in the application see abstract	1-43,46, 47,49, 53-57, 59-82,88
X	GERISCH, GUENTHER ET AL: "Chemoattractant-controlled accumulation of coronin at the leading edge of Dictyostelium cells monitored using a green fluorescent protein-coronin fusion protein" CURR. BIOL. (1995), 5(11), 1280-5 CODEN: CUBLE2:ISSN: 0960-9822, XP002089510 see abstract p 1281, right col, second full , last sentence	1,40,43,
X	SIDOROVA, JULIA M. ET AL: "Cell cycle-regulated phosphorylation of Swi6 controls its nuclear localization" MOL. BIOL. CELL (1995), 6(12), 1641-58 CODEN: MBCEEV;ISSN: 1059-1524, XP002089512 see the whole document	40,43,44
X	HAN HTUN ET AL: "VISUALIZATION OF GLUCOCORTICOID RECEPTOR TRANSLOCATION AND INTRANUCLEAR ORGANIZATION IN LIVING CELLS WITH A GREEN FLUORESCENT PROTEIN CHIMERA" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 93, no. 10, May 1996, pages 4845-4850, XP002029560 see the whole document	1-40,44, 64-72

In. atlonal Application No PCT/DK 98/00145

	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category :	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X .	CAREY K L ET AL: "EVIDENCE USING A GREEN FLUORESCENT PROTEIN-GLUCOCORTICOID RECEPTOR CHIMERA THAT THE RAN/TC4 GTPASE MEDIATES AN ESSENTIAL FUNCTION INDEPENDENT OF NUCLEAR PROTEIN IMPORT" THE JOURNAL OF CELL BIOLOGY, vol. 133, no. 5, June 1996, pages 985-996, XP000670316 cited in the application see the whole document	1-40,44, 64-72
X	OGAWA H ET AL: "LOCALIZATION, TRAFFICKING, AND TEMPERATURE-DEPENDENCE OF THE AEQUOREA GREEN FLUORESCENT PROTEIN IN CULTURES VERTEBRATE CELLS" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 92, no. 25, 5 December 1995, pages 11899-11903, XP002029556 see the whole document	1-40,44, 64-72
X	WESTPHAL, MONIKA ET AL: "Microfilament dynamics during cell movement and chemotaxis monitored using a GFP - actin fusion protein" CURR. BIOL. (1997), 7(3), 176-183 CODEN: CUBLE2; ISSN: 0960-9822, XP002090291 see page 181, left-hand column, line 1	1,40,43, 45
X	TODA, TAKASHI ET AL: "The fission yeast sts5+ gene is required for maintenance of growth polarity and functionally interacts with protein kinase C and an osmosensing MAP kinase pathway"  J. CELL SCI. (1996), 109(9), 2331-2342  CODEN: JNCSAI; ISSN: 0021-9533, XP002090292 see abstract	40,42
A	WEBB, CHRIS D. ET AL: "Use of green fluorescent protein for visualization of cell-specific gene expression and subcellular protein localization during sporulation in Bacillus subtilis"  J. BACTERIOL. (1995), 177(20), 5906-11 CODEN: JOBAAY; ISSN: 0021-9193, XP002089513 see the whole document	44
A	WO 94 23039 A (CANCER RES INST ROYAL; MARSHALL CHRISTOPHER JOHN (GB); ASHWORTH AL) 13 October 1994 see the whole document	1-84,87, 88

ational application No. PCT/DK 98/00145

Boxi	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This Inte	ernational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2. X	Although claims 83-84 and claim 87 relate to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition (Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy).  Claims Nos.:  85,86 because they relate to parts of the International Application that do not comply with the prescribed requirements to such
	an extent that no meaningful International Search can be carried out, specifically:
	see FURTHER INFORMATION sheet PCT/ISA/210
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box ii	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This Inte	ernational Searching Authority found multiple inventions in this international application, as follows:
	see additional sheet
İ	
1. X	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remar	k on Protest  X The additional search fees were accompanied by the applicant's protest.
	No protest accompanied the payment of additional search fees.
I	

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 85,86

The subject-matter (compounds per se) is solely characterised in claims 85 and 86 by the result to be achieved, no support of a technical character is derivable from the description for the technical formulation of the subject of the search, accordingly no scope of a search could be defined and a meaningfull search is hence not possible.

### FURTHER INF RMATI NC NTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 47, 49, 53-57

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being serine/threonine protein kinases

2. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 48

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to tyrosine kinases

3. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 50, 51

MMethods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to cAMP dependent protein kinases.

4. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 52

MMethods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active

# FURTHER INFORMATION C NTINUED FROM PCT/ISA/ 210

molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being cGMP dependent protein kinases

5. Claims: Partially: 1-43, 59-82 and 88; Entirely: 58

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being protein phosphatases

6. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 44

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to transcription factors

7. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 45

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to proteins associated with the cytoskeletal network

Information on patent family members

In. .iational Application No PCT/DK 98/00145

Patent document cited in search repo		Publication date		atent family member(s)	Publication date
WO 9711094		27-03-1997	AU	4482996 A	09-04-1997
			CA	2232727 A	27-03-1997
			EP	0851874 A	08-07-1998
WO 9101305	A	07-02-1991	AU	6054590 A	22-02-1991
			CA	2064766 A	23-01-1991
			EP	0484369 A	13-05-1992
			JP	5501862 T	08-04-1993
			US	5683888 A	04-11-1997
WO 9507463	Α	16-03-1995	US	5491084 A	13-02-1996
			AU	694745 B	30-07-1998
			AU	7795794 A	27-03-1995
			CA	2169298 A	16-03-1995
			EP	0759170 A	26-02-1997
			JP	9505981 T	17-06-1997
WO 9623898	Α	08-08-1996	AU	4483096 A	21-08-1996
			CA	2217700 A	08-08-1996
			EP	0815257 A •	07-01-1998
WO 9603649	Α	08-02-1996	AU	3146095 A	22-02-1996
			CA	2195629 A	08-02-1996
			EP	0772773 A	14-05-1997
			JP	10503369 T	31-03-1998
WO 9720931	Α	12-06-1997	AU	1283497 A	27~06-1997
			CA	2239951 A	12-06-1997
WO 9730074	Α	21-08-1997	AU	2272397 A	02-09-1997
WO 9802571	Α	22-01-1998	AU	3801997 A	09-02-1998
WO 9830715	Α	16-07-1998	AU	5090498 A	03-08-1998
WO 9423039	 A	13-10-1994	AU	677834 B	08-05-1997
			AU	6382394 A	24-10-1994
			EΡ	0703984 A	03-04-1996
			JP	9501302 T	10-02-1997
			AU	696939 B	24-09-1998
			AU	1586195 A	29-08-1995
			CA	2182967 A	17-08-1995
			EP	0742827 A	20-11-1996
			MO	9521923 A	17-08-1995
			JP	9508795 T	09-09-1997

### **PCT**

# WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



### INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: WO 98/45704 (11) International Publication Number: **A2** G01N 33/53 (43) International Publication Date: 15 October 1998 (15.10.98)

DK

PCT/DK98/00145 (21) International Application Number:

7 April 1998 (07.04.98) (22) International Filing Date:

(71) Applicant (for all designated States except US): NOVO

7 April 1997 (07.04.97)

NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsvaerd (DK).

(72)-Inventors; and (75) Inventors/Applicants (for US only): THASTRUP, Ole [DK/DK]; Birkevej 37, DK-3460 Birkerød (DK). PE-TERSEN BJØRN, Sara [DK/DK]; Klampenborgvej 102, DK-2800 Lyngby (DK). TULLIN, Søren [DK/DK]; Karl Gjellerups Alle 18, DK-2860 Søborg (DK). KASPER, Almholt [DK/DK]; Eigilsgade 32, 4. tv, DK-2300 Køben. havn S (DK). SCUDDER, Kurt [US/DK]; Lavendelhaven 70, DK-2830 Virum (DK).

(74) Common Representative: NOVO NORDISK A/S; attn. Lars Kellberg, Novo Allé, DK-2880 Bagsværd (DK).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: A METHOD FOR EXTRACTING QUANTITATIVE INFORMATION RELATING TO AN INFLUENCE ON A CHLLULAR RESPONSE

#### (57) Abstract

(30) Priority Data:

0392/97

Cells are genetically modified to expresss a luminophore, e.g., a modified (F64L, S65T, Y66H) Green Fluorescent Protein (GFP, EGFP) coupled to a component of an intracellular signalling pathway such as a transcription factor, a cGMP- or cAMP-dependent protein kinase, a cyclin-, calmodulin- or phospholipid-dependent or mitogen-activated serine/threonin protein kinase, a tyrosine protein kinase, or a protein phosphatase (e.g. PKA, PKC, Erk, Smad, VASP, actin, p38, Jnk1, PKG, IkappaB, CDK2, Grk5, Zap70, p85, protein-tyrosine phosphatase 1C, Stat5, NFAT, NFkappaB, RhoA, PKB). An influence modulates the intracellular signalling pathway in such a way that the luminophore is being redistributed or translocated with the component in living cells in a manner experimentally determined to be correlated to the degree of the influence. Measurement of redistribution is performed by recording of light intensity, fluorescence lifetime, polarization, wavelength shift, resonance energy transfer, or other properties by an apparatus consisting of e.g. a fluorescence microscope and a CCD camera. Data stored as digital images are processed to numbers representing the degree of redistribution. The method can be used as a screening program for identifying a compound that modulates a component and is capable of treating a disease related to the function of the component.

### FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AĽ	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
ΑU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaljan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinca	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	. Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA.	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
cz	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

WO 98/45704 PCT/DK98/00145

1

A METHOD for extracting quantitative information relating to an influence on a cellular response

#### FIELD OF INVENTION

The present invention relates to a method and tools for extracting quantitative information relating to an influence, on a cellular response, in particular an influence caused by contacting or incubating the cell with a substance influencing a cellular response, where the cellular response is manifested in redistribution of at least one component in the cell. In particular, the invention relates to a method for extracting quantitative information relating to an influence on an intracellular pathway involving redistribution of at least one component associated with the pathway. The method of the invention may be used as a very efficient procedure for testing or discovering the influence of a substance on a physiological process, for example in connection with screening for new drugs, testing of substances for toxicity, identifying drug targets for known or novel drugs. Other valuable uses of the method and technology of the invention will be apparent to the skilled person on the basis of the following disclosure. In a particular embodiment of the invention, the present invention relates to a method of detecting intracellular translocation or redistribution of biologically active polypeptides, preferably an enzyme, affecting intracellular processes, and a DNA construct and a cell for use in the method.

20

25

30

g

5

10

15

#### BACKGROUND OF THE INVENTION

Intracellular pathways are tightly regulated by a cascade of components that undergo modulation in a temporally and spatially characteristic manner. Several disease states can be attributed to altered activity of individual signalling components (i.e. protein kinases, protein phosphatases, transcription factors). These components therefore render themselves as attractive targets for therapeutic intervention.

Protein kinases and phosphatases are well described components of several intracellular signalling pathways. The catalytic activity of protein kinases and phosphatases are assumed to play a role in virtually all regulatable cellular processes. Although the involvement of protein kinases in cellular signalling and regulation have been subjected to extensive studies, detailed knowledge on e.g. the exact timing and spatial characteristics of signalling events is often difficult to obtain due to lack of a convenient technology.

15

20

25

30

2

Novel ways of monitoring specific modulation of intracellular pathways in intact, living cells is assumed to provide new opportunities in drug discovery, functional genomics, toxicology, patient monitoring etc.

The spatial orchestration of protein kinase activity is likely to be essential for the high degree of specificity of individual protein kinases. The phosphorylation mediated by protein kinases is balanced by phosphatase activity. Also within the family of phosphatases translocation has been observed, e.g. translocation of PTP2C to membrane ruffles [(Cossette *et al.*1996)], and likewise is likely to be indicative of phosphatase activity.

Protein kinases often show a specific intracellular distribution before, during and after activation. Monitoring the translocation processes and/or redistribution of individual protein kinases or subunits thereof is thus likely to be indicative of their functional activity. A connection between translocation and catalytic activation has been shown for protein kinases like the diacyl glycerol (DAG)-dependent protein kinase C (PKC), the cAMP-dependent protein kinase (PKA) [(DeBernardi *et al.*1996)] and the mitogen-activated-protein kinase Erk-1 [(Sano *et al.*1995)].

Commonly used methods of detection of intracellular localisation/activity of protein kinases and phosphatases are immunoprecipitation, Western blotting and immunocytochemical detection.

Taking the family of diacyl glycerol (DAG)-dependent protein kinase Cs (PKCs) as an example, it has been shown that individual PKC isoforms that are distributed among different tissues and cells have different activator requirements and undergo differential translocation in response to activation. Catalytically inactive DAG-dependent PKCs are generally distributed throughout the cytoplasm, whereas they upon activation translocate to become associated with different cellular components, e.g. plasma membrane [(Farese, 1992),(Fulop Jr. et al.1995)] nucleus [(Khalil et al.1992)], cytoskeleton [(Blobe et al.1996)]. The translocation phenomenon being indicative of PKC activation has been monitored using different approaches: a) immunocytochemistry where the localisation of individual isoforms can be detected after permeabilisation and fixation of the cells [(Khalil et al.1992)]; and b) tagging all DAG-dependent PKC isoforms with a fluorescently labelled phorbol myristate acetate (PMA) [(Godson et al.1996)]; and c) chemical tagging PKC b1 with the fluorophore Cy3 [(Bastiaens & Jovin 1996)] and d) genetic tagging of PKCα ([Schrnidt et al. 1997]) and of PKCγ and PKC ε ([Sakai et al. 1996]). The first method does not provide dynamic information whereas the latter methods will. Tagging PKC with fluorescently labelled phorbol myristate acetate cannot

25

30

distinguish between different DAG-dependent isoforms of PKC but will label and show movement of all isoforms. Chemical and genetic labelling of specific DAG-dependent PKCs confirmed that they in an isoform specific manner upon activation move to cell periphery or nucleus.

In an alternative method, protein kinase A activity has been measured in living cells by chemical labelling one of the kinase's subunit (Adams et al.1991). The basis of the methodology is that the regulatory and catalytic subunit of purified protein kinase A is labelled with fluorescein and rhodamine, respectively. At low cAMP levels protein kinase A is assembled in a heterotetrameric form which enables fluorescence resonance energy transfer between the two fluorescent dyes. Activation of protein kinase A leads to dissociation of the complex, thereby eliminating the energy transfer. A disadvantage of this technology is that the labelled protein kinase A has to be microinjected into the cells of interest. This highly invasive technique is cumbersome and not applicable to large scale screening of biologically active substances. A further disadvantage of this technique as compared to the presented invention is that the labelled protein kinase A cannot be inserted into organisms/animals as a transgene.

Recently it was discovered that Green Fluorescent Protein (GFP) expressed in many different cell types, including mammalian cells, became highly fluorescent [(Chalfie et al. 1994)]. WO95/07463 describes a cell capable of expressing GFP and a method for detecting a protein of interest in a cell based on introducing into a cell a DNA molecule having DNA sequence encoding the protein of interest linked to DNA sequence encoding a GFP such that the protein produced by the DNA molecule will have the protein of interest fused to the GFP, then culturing the cells in conditions permitting expression of the fused protein and detecting the location of the fluorescence in the cell, thereby localizing the protein of interest in the cell. However, examples of such fused proteins are not provided, and the use of fusion proteins with GFP for detection or quantitation of translocation or redistribution of biologically active polypeptides affecting intracellular processes upon activation, such as proteins involved in signalling pathways, e.g. protein kinases or phosphatases, has not been suggested. WO 95/07463 further describes cells useful for the detection of molecules, such as hormones or heavy metals, in a biological sample, by operatively linking a regulatory element of the gene which is affected by the molecule of interest to a GFP, the presence of the molecules will affect the regulatory element which in turn will affect the expression of the GFP. In this way the gene encoding GFP is used as a reporter gene in a cell which is constructed for monitoring the presence of a specific molecular identity.

Green Fluorescent Protein has been used in an assay for the detection of translocation of the glucocorticoid receptor (GR) [Carey, KL et al., The Journal of Cell Biology, Vol. 133, No. 5, p. 985-996 (1996)]. A GR-S65TGFP fusion has been used to study the mechanisms involved in translocation of the glucocorticoid receptor (GR) in response to the agonist dexamethasone from the cytosol, where it is present in the absence of a ligand, through the nuclear pore to the nucleus where it remains after ligand binding. The use of a GR-GFP fusion enables real-time imaging and quantitation of nuclear/cytoplasmic ratios of the fluorescence signal.

Many currently used screening programmes designed to find compounds that affect protein kinase activity are based on measurements of kinase phosphorylation of artificial or natural substrates, receptor binding and/or reporter gene expression.

#### DISCLOSURE OF THE INVENTION

5

15

20

The present invention provides an important new dimension in the investigation of cellular systems involving redistribution in that the invention provides quantification of the redistribution responses or events caused by an influence, typically contact with a chemical substance or mixture of chemical substances, but also changes in the physical environment. The quantification makes it possible to set up meaningful relationships, expressed numerically, or as curves or graphs, between the influences (or the degree of influences) on cellular systems and the redistribution response. This is highly advantageous because, as has been found, the quantification can be achieved in both a fast and reproducible manner, and - what is perhaps even more important - the systems which become quantifiable utilizing the method of the invention are systems from which enormous amounts of new information and insight can be derived.

The present screening assays have the distinct advantage over other screening assays, e.g., receptor binding assays, enzymatic assays, and reporter gene assays, in providing a system in which biologically active substances with completely novel modes of action, e.g. inhibition or promotion of redistribution/translocation of a biologically active polypeptide as a way of regulating its action rather than inhibition/activation of enzymatic activity, can be identified in a way that insures very high selectivity to the particular isoform of the biologically active polypeptide and further development of compound selectivity versus other isoforms of

the same biologically active polypeptide or other components of the same signalling pathway.

In its broadest aspect, the invention relates to a method for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on a mechanically intact living cell or mechanically intact living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cell or cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, the association resulting in a modulation of the luminescence characteristics of the luminophore, detecting and recording the spatially distributed light from the luminophore, and processing the recorded variation in the spatially distributed light to provide quantitative information correlating the spatial distribution or change in the spatial distribution to the degree of the influence. In a preferred embodiment of the invention the luminophore, which is present in the cell or cells, is capable of being redistributed by modulation of an intracellular pathway, in a manner which is related to the redistribution of at least one component of the intracellular pathway. In another preferred embodiment of the invention, the luminophore is a fluorophore.

#### The cells

5

10

15

25

30

In the invention the cell and/or cells are mechanically intact and alive throughout the experiment. In another embodiment of the invention, the cell or cells is/are fixed at a point in time after the application of the influence at which the response has been predetermined to be significant, and the recording is made at an arbitrary later time.

The mechanically intact living cell or cells could be selected from the group consisting of fungal cell or cells, such as a yeast cell or cells; invertebrate cell or cells including insect cell or cells; and vertebrate cell or cells, such as mammalian cell or cells. This cell or these cells is/are incubated at a temperature of 30°C or above, preferably at a temperature of from 32°C to 39°C, more preferably at a temperature of from 35°C to 38°C, and most preferably at a temperature of about 37°C during the time period over which the influence is observed. In one aspect of the invention the mechanically intact living cell is part of a matrix of identical or non-identical cells.

A cell used in the present invention should contain a nucleic acid construct encoding a fusion polypeptide as defined herein and be capable of expressing the sequence encoded by the construct. The cell is a eukaryotic cell selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells including insect cells; vertebrate cells such as mammalian cells. The preferred cells are mammalian cells.

In another aspect of the invention the cells could be from an organism carrying in at least one of its component cells a nucleic acid sequence encoding a fusion polypeptide as defined herein and be capable of expressing said nucleic acid sequence. The organism is selected from the group consisting of unicellular and multicellular organisms, such as a mammal.

10

15

20

5

#### The luminophore

The luminophore is the component which allows the redistribution to be visualised and/or recorded by emitting light in a spatial distribution related to the degree of influence. In one embodiment of the invention, the luminophore is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence. In another embodiment, the luminophore is capable of associating with a component which is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence. In another embodiment, the luminophore correlation between the redistribution of the luminophore and the degree of the influence could be determined experimentally. In a preferred aspect of the invention, the luminophore is capable of being redistributed in substantially the same manner as the at least one component of an intracellular pathway. In yet another embodiment of the invention, the luminophore is capable of being quenched upon spatial association with a component which is redistributed by modulation of the pathway, the quenching being measured as a change in the intensity of the luminescence.

The luminophore could be a fluorophore. In a preferred embodiment of the invention, the luminophore could be a polypeptide encoded by and expressed from a nucleotide sequence harboured in the cell or cells. The luminophore could be a hybrid polypeptide comprising a fusion of at least a portion of each of two polypeptides one of which comprises a luminescent polypeptide and the other one of which comprises a biologically active polypeptide, as defined herein.

The luminescent polypeptide could be a GFP as defined herein or could be selected from the group consisting of green fluorescent proteins having the F64L mutation as defined herein

such as F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP. The GFP could be N- or C-terminally tagged, optionally via a peptide linker, to the biologically active polypeptide or a part or a subunit thereof. The fluorescent probe could be a component of a intracellular signalling pathway. The probe is coded for by a nucleic acid construct.

The pathway of investigation in the present invention could be an intracellular signalling pathway.

#### The influence

In a preferred embodiment of the invention, the influence could be contact between the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance and/or incubation of the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance. The influence will modulate the intracellular processes. In one aspect the modulation could be an activation of the intracellular processes. In another aspect the modulation could be an deactivation of the intracellular processes. In yet another aspect, the influence could inhibit or promote the redistribution without directly affecting the metabolic activity of the component of the intracellular processes.

In one embodiment the invention is used as a basis for a screening program, where the effect of unknown influences such as a compound library, can be compared to influence of known reference compounds under standardised conditions.

20

25

30

10

15

#### The recording

In addition to the intensity, there are several parameters of fluorescence or luminescence which can be modulated by the effect of the influence on the underlying cellular phenomena, and can therefore be used in the invention. Some examples are resonance energy transfer, fluorescence lifetime, polarisation, wavelength shift. Each of these methods requires a particular kind of filter in the emission light path to select the component of the light desired and reject other components. The recording of property of light could be in the form of an ordered array of values such as a CCD array or a vacuum tube device such as a vidicon tube.

In one embodiment of the invention, the spatially distributed light emitted by a luminophore could be detected by a change in the resonance energy transfer between the luminophore and another luminescent entity capable of delivering energy to the luminophore, each of

10

15

20

25

30

which has been selected or engineered to become part of, bound to or associated with particular components of the intracellular pathway. In this embodiment, either the luminophore or the luminescent entity capable of delivering energy to the luminophore undergoes redistribution in response to an influence. The resonance energy transfer would be measured as a change in the intensity of emission from the luminophore, preferably sensed by a single channel photodetector which responds only to the average intensity of the luminophore in a non-spatially resolved fashion.

In one embodiment of the invention, the recording of the spatially distributed light could be made at a single point in time after the application of the influence. In another embodiment, the recording could be made at two points in time, one point being before, and the other point being after the application of the influence. The result or variation is determined from the change in fluorescence compared to the fluorescence measured prior to the influence or modulation. In another embodiment of the invention, the recording could be performed at a series of points in time, in which the application of the influence occurs at some time after the first time point in the series of recordings, the recording being performed, e.g., with a predetermined time spacing of from 0.1 seconds to 1 hour, preferably from 1 to 60 seconds, more preferably from 1 to 30 seconds, in particular from 1 to 10 seconds, over a time span of from 1 second to 12 hours, such as from 10 seconds to 12 hours, e.g., from 10 seconds to one hour, such as from 60 seconds to 30 minutes or 20 minutes. The result or variation is determined from the change in fluorescence over time. The result or variation could also be determined as a change in the spatial distribution of the fluorescence over time.

#### **Apparatus**

The recording of spatially distributed luminescence emitted from the luminophore is performed by an apparatus for measuring the distribution of fluorescence in the cell or cells, and thereby any change in the distribution of fluorescence in the cell or cells, which includes at a minimum the following component parts: (a) a light source, (b) a method for selecting the wavelength(s) of light from the source which will excite the fluorescence of the protein, (c) a device which can rapidly block or pass the excitation light into the rest of the system, (d) a series of optical elements for conveying the excitation light to the specimen, collecting the emitted fluorescence in a spatially resolved fashion, and forming an image from this fluorescence emission, (e) a bench or stand which holds the container of the cells being measured in a predetermined geometry with respect to the series of optical elements, (f) a detector to

10

20

25

30

record the spatially resolved fluorescence in the form of an image, (g) a computer or electronic system and associated software to acquire and store the recorded images, and to compute the degree of redistribution from the recorded images.

In a preferred embodiment of the invention the apparatus system is automated. In one embodiment the components in d and e mentioned above comprise a fluorescence microscope. In one embodiment the component in f mentioned above is a CCD camera.

In one embodiment the image is formed and recorded by an optical scanning system.

In one embodiment a liquid addition system is used to add a known or unknown compound to any or all of the cells in the cell holder at a time determined in advance. Preferably, the liquid addition system is under the control of the computer or electronic system. Such an automated system can be used for a screening program due to its ability to generate results from a larger number of test compounds than a human operator could generate using the apparatus in a manual fashion.

#### 15 Quantitation of the influence

The recording of the variation or result with respect to light emitted from the luminophore is performed by recording the spatially distributed light as one or more digital images, and the processing of the recorded variation to reduce it to one or more numbers representative of the degree of redistribution comprises a digital image processing procedure or combination of digital image processing procedures. The quantitative information which is indicative of the degree of the cellular response to the influence or the result of the influence on the intracellular pathway is extracted from the recording or recordings according to a predetermined calibration based on responses or results, recorded in the same manner, to known degrees of a relevant specific influence. This calibration procedure is developed according to principles described below (Developing an Image-based Assay Technique). Specific descriptions of the procedures for particular assays are given in the examples.

While the stepwise procedure necessary to reduce the image or images to the value representative of the is particular to each assay, the individual steps are generally well-known methods of image processing. Some examples of the individual steps are point operations such as subtraction, ratioing, and thresholding, digital filtering methods such as smoothing, sharpening, and edge detection, spatial frequency methods such as Fourier filtering, image cross-correlation and image autocorrelation, object finding and classification (blob analysis),

and colour space manipulations for visualisation. In addition to the algorithmic procedures, heuristic methods such as neural networks may also be used.

#### **Nucleic acid constructs**

- The nucleic acid constructs used in the present invention encode in their nucleic acid sequences fusion polypeptides comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and a GFP, preferably an F64L mutant of GFP, N- or C-terminally fused, optionally via a peptide linker, to the biologically active polypeptide or part thereof.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein kinase or a phosphatase.
  - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a transcription factor or a part thereof which changes cellular localisation upon activation.
  - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein, or a part thereof, which is associated with the cytoskeletal network and which changes cellular localisation upon activation.
    - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein kinase or a part thereof which changes cellular localisation upon activation.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
  - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a tyrosine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a phospholipid-dependent serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
  - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cAMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation. In a preferred embodiment the biologically active polypeptide encoded by the nucleic acid construct is a PKAc-F64L-S65T-GFP fusion.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cGMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a calmodulin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a mitogen-activated serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation. In preferred embodiments the biologically active polypeptide encoded by the nucleic acid constructs are an ERK1-F64L-S65T-GFP fusion or an EGFP-ERK1 fusion.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cyclin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein phosphatase or a part thereof capable of changing cellular localisation upon activation.

In one preferred embodiment of the invention the nucleic acid constructs may be DNA constructs.

- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct In one embodiment the gene encoding GFP in the nucleic acid construct is derived from Aequorea victoria. In a preferred embodiment the gene encoding GFP in the nucleic acid construct is EGFP or a GFP variant selected from F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP.
- In preferred embodiments of the invention the DNA constructs which can be identified by any of the DNA sequences shown in SEQ ID NO: 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142 or are variants of these sequences capable of encoding the same fusion polypeptide or a fusion polypeptide which is biologically equivalent thereto, e.g. an isoform, or a splice variant or a homologue from another species.

10

15

20

25

12

#### Screening program

The present invention describes a method that may be used to establish a screening program for the identification of biologically active substances that directly or indirectly affects intracellular signalling pathways and because of this property are potentially useful as medicaments. Based on measurements in living cells of the redistribution of spatially resolved luminescence from luminophores which undergo a change in distribution upon activation or deactivation of an intracellular signalling pathway the result of the individual measurement of each substance being screened indicates its potential biological activity.

In one embodiment of the invention the screening program is used for the identification of a biologically toxic substance as defined herein that exerts its toxic effect by interfering with an intracellular signalling pathway. Based on measurements in living cells of the redistribution of spatially resolved luminescence from luminophores which undergo a change in distribution upon activation or deactivation of an intracellular signalling pathway the result of the individual measurement of each substance being screened indicates its potential biologically toxic activity. In one embodiment of a screening program a compound that modulates a component of an intracellular pathway as defined herein, can be found and the therapeutic amount of the compound estimated by a method according to the method of the invention. In a preferred embodiment the present invention leads to the discovery of a new way of treating a condition or disease related to the intracellular function of a biologically active polypeptide comprising administration to a patient suffering from said condition or disease of an effective amount of a compound which has been discovered by any method according to the invention. In another preferred embodiment of the invention a method is established for identification of a new drug target or several new drug targets among the group of biologically active polypeptides which are components of intracellular signalling pathways.

In another embodiment of the invention an individual treatment regimen is established for the selective treatment of a selected patient suffering from an ailment where the available medicaments used for treatment of the ailment are tested on a relevant primary cell or cells obtained from said patient from one or several tissues, using a method comprising transfecting the cell or cells with at least one DNA sequence encoding a fluorescent probe according to the invention, transferring the transfected cell or cells back the said patient, or culturing the cell or cells under conditions permitting the expression of said probes and exposing it to an array of the available medicaments, then comparing changes in fluorescence patterns or redistribution patterns of the fluorescent probes in the intact living cell or cells to

detect the cellular response to the specific medicaments (obtaining a cellular action profile), then selecting one or more medicament or medicaments based on the desired activity and acceptable level of side effects and administering an effective amount of these medicaments to the selected patient.

5

10

20

25

30

## Back-tracking of a signal transduction pathway

The present invention describes a method that may be used to establish a screening program for back-tracking signal transduction pathways as defined herein. In one embodiment the screening program is used to establish more precisely at which level one or several compounds affect a specific signal transduction pathway by successively or in parallel testing the influence of the compound or compounds on the redistribution of spatially resolved luminescence from several of the luminophores which undergo a change in distribution upon activation or deactivation of the intracellular signalling pathway under study.

### 15 Construction and testing of probes

In general, a probe, i.e. a "GeneX"-GFP fusion or a GFP-"GeneX" fusion, is constructed using PCR with "GeneX"-specific primers followed by a cloning step to fuse "GeneX" in frame with GFP. The fusion may contain a short vector derived sequence between "GeneX" and GFP (e.g. part of a multiple cloning site region in the plasmid) resulting in a peptide linker between "GeneX" and GFP in the resulting fusion protein.

#### Detailed stepwise procedure:

- Identifying the sequence of the gene. This is most readily done by searching a depository of genetic information, e.g. the GenBank Sequence Database, which is widely available and routinely used by molecular biologists. In the specific examples below the GenBank Accession number of the gene in question is provided.
- Design of gene-specific primers. Inspection of the sequence of the gene allows design of gene-specific primers to be used in a PCR reaction. Typically, the top-strand primer encompasses the ATG start codon of the gene and the following ca. 20 nucleotides, while the bottom-strand primer encompasses the stop codon and the ca. 20 preceding nucleotides, if

the gene is to be fused behind GFP, i.e. a GFP-"GeneX" fusion. If the gene is to be fused in front of GFP, i.e. a "GeneX"-GFP fusion, a stop codon must be avoided. Optionally, the full length sequence of GeneX may not be used in the fusion, but merely the part which localizes and redistributes like GeneX in response to a signal.

5

10

25

30

In addition to gene-specific sequences, the primers contain at least one recognition sequence for a restriction enzyme, to allow subsequent cloning of the PCR product. The sites are chosen so that they are unique in the PCR product and compatible with sites in the cloning vector. Furthermore, it may be necessary to include an exact number of nucleotides between the restriction enzyme site and the gene-specific sequence in order to establish the correct reading frame of the fusion gene and/or a translation initiation consensus sequence. Lastly, the primers always contain a few nucleotides in front of the restriction enzyme site to allow efficient digestion with the enzyme.

- -Identifying a source of the gene to be amplified. In order for a PCR reaction to produce a product with gene-specific primers, the gene-sequence must initially be present in the reaction, e.g. in the form of cDNA. Information in GenBank or the scientific literature will usually indicate in which tissue(s) the gene is expressed, and cDNA libraries from a great variety of tissues or cell types from various species are commercially available, e.g. from Clontech
   (Palo Alto), Stratagene (La Jolla) and Invitrogen (San Diego). Many genes are also available in cloned form from The American Type Tissue Collection (Virginia).
  - Optimizing the PCR reaction. Several factors are known to influence the efficiency and specificity of a PCR reaction, including the annealing temperature of the primers, the concentration of ions, notably Mg<sup>2+</sup> and K<sup>+</sup>, present in the reaction, as well as pH of the reaction. If the result of a PCR reaction is deemed unsatisfactory, it might be because the parameters mentioned above are not optimal. Various annealing temperatures should be tested, e.g. in a PCR machine with a built-in temperature gradient, available from e.g. Stratagene (La Jolla), and/or various buffer compositions should be tried, e.g. the OptiPrime buffer system from Stratagene (La Jolla).

- Cloning the PCR product. The vector into which the amplified gene product will be cloned and fused with GFP will already have been taken into consideration when the primers were designed. When choosing a vector, one should at least consider in which cell types the probe subsequently will be expressed, so that the promoter controlling expression of the probe is compatible with the cells. Most expression vectors also contain one or more selective markers, e.g. conferring resistance to a drug, which is a useful feature when one wants to make stable transfectants. The selective marker should also be compatible with the cells to be used.
- The actual cloning of the PCR product should present no difficulty as it typically will be a one-step cloning of a fragment digested with two different restriction enzymes into a vector digested with the same two enzymes. If the cloning proves to be problematic, it may be because the restriction enzymes did not work well with the PCR fragment. In this case one could add longer extensions to the end of the primers to overcome a possible difficulty of digestion close to a fragment end, or one could introduce an intermediate cloning step not based on restriction enzyme digestion. Several companies offer systems for this approach, e.g. Invitrogen (San Diego) and Clontech (Palo Alto).
- Once the gene has been cloned and, in the process, fused with the GFP gene, the resulting product, usually a plasmid, should be carefully checked to make sure it is as expected. The most exact test would be to obtain the nucleotide sequence of the fusion-gene.

#### Testing the probe

Once a DNA construct for a probe has been generated, its functionality and usefulness may be tested by subjecting it to the following tests:

- Transfecting it into cells capable of expressing the probe. The fluorescence of the cell is inspected soon after, typically the next day. At this point, two features of cellular fluorescence are noted: the intensity and the sub-cellular localization.

25

5

25

30

The intensity should usually be at least as strong as that of unfused GFP in the cells. If it is not, the sequence or quality of the probe-DNA might be faulty, and should be carefully checked.

The sub-cellular localization is an indication of whether the probe is likely to perform well. If it 5 localizes as expected for the gene in question, e.g. is excluded from the nucleus, it can immediately go on to a functional test. If the probe is not localized soon after the transfection procedure, it may be because of overexpression at this point in time, as the cell typically will have taken of very many copies of the plasmid, and localization will occur in time, e.g. within 10 a few weeks, as plasmid copy number and expression level decreases. If localization does not occur after prolonged time, it may be because the fusion to GFP has destroyed a localization function, e.g. masked a protein sequence essential for interaction with its normal cellular anchor-protein. In this case the opposite fusion might work, e.g. if GeneX-GFP does not work, GFP-GeneX might, as two different parts of GeneX will be affected by the proximity to GFP. If this does not work, the proximity of GFP at either end might be a problem, and it 15 could be attempted to increase the distance by incorporating a longer linker between GeneX and GFP in the DNA construct.

If there is no prior knowledge of localization, and no localization is observed, it may be because the probe should not be localized at this point, because such is the nature of the protein fused to GFP. It should then be subjected to a functional test.

In a functional test, the cells expressing the probe are treated with at least one compound known to perturb, usually by activating, the signalling pathway on which the probe is expected to report by redistributing itself within the cell. If the redistribution is as expected, e.g. if prior knowledge tell that it should translocate from location X to location Y, it has passed the first critical test. In this case it can go on to further characterization and quantification of the response.

If it does not perform as expected, it may be because the cell lacks at least one component of the signalling pathway, e.g. a cell surface receptor, or there is species incompatibility, e.g. if the probe is modelled on sequence information of a human geneproduct, and the cell is of hamster origin. In both instances one should identify other cell types for the testing process where these potential problems would not apply.

WO 98/45704

5

10

15

20

25

30

17

If there is no prior knowledge about the pattern of redistribution, the analysis of the redistribution will have to be done in greater depth to identify what the essential and indicative features are, and when this is clear, it can go on to further characterization and quantification of the response. If no feature of redistribution can be identified, the problem might be as mentioned above, and the probe should be retested under more optimal cellular conditions.

If the probe does not perform under optimal cellular conditions it's back to the drawing board.

#### Developing an image-based assay technique

The process of developing an image-based redistribution assay begins with either the unplanned experimental observation that a redistribution phenomenon can be visualised, or the design of a probe specifically to follow a redistribution phenomenon already known to occur. In either event, the first and best exploratory technique is for a trained scientist or technician to observe the phenomenon. Even with the rapid advances in computing technology, the human eye-brain combination is still the most powerful pattern recognition system known, and requires no advance knowledge of the system in order to detect potentially interesting and useful patterns in raw data. This is especially if those data are presented in the form of images, which are the natural "data type" for human visual processing. Because human visual processing operates most effectively in a relatively narrow frequency range, i.e., we cannot see either very fast or very slow changes in our visual field, it may be necessary to record the data and play it back with either time dilation or time compression.

Some luminescence phenomena cannot be seen directly by the human eye. Examples include polarization and fluorescence lifetime. However, with suitable filters or detectors, these signals can be recorded as images or sequences of images and displayed to the human in the fashion just described. In this way, patterns can be detected and the same methods can be applied.

Once the redistribition has been determined to be a reproducible phenomenon, one or more data sets are generated for the purpose of developing a procedure for extracting the quantitative information from the data. In parallel, the biological and optical conditions are determined which will give the best quality raw data for the assay. This can become an iterative process; it may be necessary to develop a quantitative procedure in order to assess the effect on the assay of manipulating the assay conditions.

15

20

25

30

The data sets are examined by a person or persons with knowledge of the biological phenomenon and skill in the application of image processing techniques. The goal of this exercise is to determine or at least propose a method which will reduce the image or sequence of images constituting the record of a "response" to a value corresponding to the degree of the response. Using either interactive image processing software or an image processing toolbox and a programming language, the method is encoded as a procedure or algorithm which takes the image or images as input and generates the degree of response (in any units) as its output. Some of the criteria for evaluating the validity of a particular procedure are:

- Does the degree of the response vary in a biologically significant fashion, i.e., does it show the known or putative dependence on the concentration of the stimulating agent or condition?
- Is the degree of response reproducible, i.e., does the same concentration or level of stimulating agent or condition give the same response with an acceptable variance?
- Is the dynamic range of the response sufficient for the purpose of the assay? If not,
   can a change in the procedure or one of its parameters improve the dynamic range?
- Does the procedure exhibit any clear "pathologies", i.e., does it give ridiculous values
  for the response if there are commonly occurring imperfections in the imaging process? Can these pathologies be eliminated, controlled, or accounted for?
- Can the procedure deal with the normal variation in the number and/or size of cells in an image?

In some cases the method may be obvious; in others, a number of possible procedures may suggest themselves. Even if one method appears clearly superior to others, optimisation of parameters may be required. The various procedures are applied to the data set and the criteria suggested above are determined, or the single procedure is applied repeatedly with adjustment of the parameter or parameters until the most satisfactory combination of signal, noise, range, etc. are arrived at. This is equivalent to the calibration of any type of single-channel sensor.

The number of ways of extracting a single value from an image are extremely large, and thus an intelligent approach must be taken to the initial step of reducing this number to a small, finite number of possible procedures. This is not to say that the procedure arrived at is

15

20

25

30

necessarily the best procedure - but a global search for the best procedure is simply out of the question due to the sheer number of possibilities involved.

Image-based assays are no different than other assay techniques in that their usefulness is characterised by parameters such as the specificity for the desired component of the sample, the dynamic range, the variance, the sensitivity, the concentration range over which the assay will work, and other such parameters. While it is not necessary to characterise each and every one of these before using the assay, they represent the only way to compare one assay with another.

#### 10 Example: Developing a Quantitative assay for GLUT4 Translocation

GLUT4 is a member of the class of glucose transporter molecules which are important in cellular glucose uptake. It is known to translocate to the plasma membrane under some conditions of stimulation of glucose uptake. The ability to visualize the glucose uptake response noninvasively, without actually measuring glucose uptake, would be a very useful assay for anyone looking for, for example, treatments for type II diabetes.

A CHO cell line which stably expressed the human insulin receptor was used as the basis for a new cell line which stably expressed a fusion between GLUT4 and GFP. This cell line was expected to show translocation of GLUT4 to the plasma membrane as visualized by the movement of the GFP. The translocation could definitely be seen in the form of the appearance of local increases in the fluorescence in regions of the plasma membrane which had a characteristic shape or pattern. This is shown in Figure 12.

These objects became known as "snircles", and the phenomenon of their appearance as "snircling". In order to quantitate their appearance, a method had to be found to isolate them as objects in the image field, and then enumerate them, measure their area, or determine some parameter about them which correlated in a dose-dependent fashion with the concentration of insulin to which the cells had been exposed. In order to separate the snircles, a binarization procedure was applied in which one copy of the image smoothed with a relatively severe gaussian kernel (sigma = 2.5) was subtracted from another copy to which only a relatively light gaussian smooth had been applied (sigma=0.5). The resultant image was rescaled to its min/max range, and an automatic threshold was applied to divide the image into two levels. The thresholded image contains a background of one value all found object with another value. The found objects were first filtered through a filter to remove objects far too

large and far too small to be snircles. The remaining objects, which represent snircles and other artifacts from the image with approximately the same size and intensity characteristics as snircles, are passed into a classification procedure which has been previously trained with many images of snircles to recognize snircles and exclude the other artifacts. The result of this procedure is a binary image which shows only the found snircles to the degree to which the classification procedure can accurately identify them. The total area of the snircles is then summed and this value is the quantitative measure of the degree of snircling for that image.

#### 10 Definitions:

5

15

20

25

30

In the present specification and claims, the term "an influence" covers any influence to which the cellular response comprises a redistribution. Thus, e.g., heating, cooling, high pressure, low pressure, humidifying, or drying are influences on the cellular response on which the resulting redistribution can be quantified, but as mentioned above, perhaps the most important influences are the influences of contacting or incubating the cell or cells with substances which are known or suspected to exert and influence on the cellular response involving a redistribution contribution. In another embodiment of the invention the influence could be substances from a compound drug library.

In the present context, the term "green fluorescent protein" is intended to indicate a protein which, when expressed by a cell, emits fluorescence upon exposure to light of the correct excitation wavelength (cf. [(Chalfie et al.1994)]). In the following, GFP in which one or more amino acids have been substituted, inserted or deleted is most often termed "modified GFP". "GFP" as used herein includes wild-type GFP derived from the jelly-fish-Aequorea victoria and modifications of GFP, such as the blue fluorescent variant of GFP disclosed by Heim et al. (1994). Proc.Natl.Acad.Sci. 91:12501, and other modifications that change the spectral properties of the GFP fluorescence, or modifications that exhibit increased fluorescence when expressed in cells at a temperature above about 30°C described in PCT/DK96/00051, published as WO 97/11094 on 27 March 1997 and hereby incorporated by reference, and which comprises a fluorescent protein derived from Aequorea Green Fluorescent Protein (GFP) or any functional analogue thereof, wherein the amino acid in position 1 upstream from the chromophore has been mutated to provide an increase of fluorescence intensity when the

10

20

25

30

fluorescent protein of the invention is expressed in cells. Preferred GFP variants are F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP. An especially preferred variant of GFP for use in all the aspects of this invention is EGFP (DNA encoding EGFP which is a F64L-S65T variant with codons optimized for expression in mammalian cells is available from Clontech, Palo Alto, plasmids containing the EGFP DNA sequence, cf. GenBank Acc. Nos. U55762, U55763).

The term "intracellular signalling pathway" and "signal transduction pathway" are intended to indicate the coordinated intracellular processes whereby a living cell transduce an external or internal signal into cellular responses. Said signal transduction will involve an enzymatic reaction said enzymes include but are not limited to protein kinases, GTPases, ATPases, protein phosphatases, phospholipases. The cellular responses include but are not limited to gene transcription, secretion, proliferation, mechanical activity, metabolic activity, cell death.

The term "second messenger" is used to indicate a low molecular weight component involved in the early events of intracellular signal transduction pathways.

The term "luminophore" is used to indicate a chemical substance which has the property of emitting light either inherently or upon stimulation with chemical or physical means. This includes but is not limited to fluorescence, bioluminescence, phosphorescence, chemiluminescence.

The term "mechanically intact living cell" is used to indicate a cell which is considered living according to standard criteria for that particular type of cell such as maintenance of normal membrane potential, energy metabolism, proliferative capability, and has not experienced any physically invasive treatment designed to introduce external substances into the cell such as microinjection.

The term "physiologically relevant" ,when applied to an experimentally determined redistribution of an intracellular component, as measured by a change in the luminescence properties or distribution, is used to indicate that said redistribution can be explained in terms of the underlying biological phenomenon which gives rise to the redistribution.

15

20

25

30

Th terms "image processing" and "image analysis" are used to describe a large family of digital data analysis techniques or combination of such techniques which reduce ordered arrays of numbers (images) to quantitative information describing those ordered arrays of numbers. When said ordered arrays of numbers represent measured values from a physical process, the quantitative information derived is therefore a measure of the physical process.

The term "fluorescent probe" is used to indicate a fluorescent fusion polypeptide comprising a GFP or any functional part thereof which is N- or C-terminally fused to a biologically active polypeptide as defined herein, optionally via a peptide linker consisting of one or more amino acid residues, where the size of the linker peptide in itself is not critical as long as the desired functionality of the fluorescent probe is maintained. A fluorescent probe according to the invention is expressed in a cell and basically mimics the physiological behaviour of the biologically active polypeptide moiety of the fusion polypeptide.

The term "mammalian cell" is intended to indicate any living cell of mammalian origin. The cell may be an established cell line, many of which are available from The American Type Culture Collection (ATCC, Virginia, USA) or a primary cell with a limited life span derived from a mammalian tissue, including tissues derived from a transgenic animal, or a newly established immortal cell line derived froma mammalian tissue including transgenic tissues, or a hybrid cell or cell line derived by fusing different celltypes of mammalian origin e.g. hybridoma cell lines. The cells may optionally express one or more non-native gene products, e.g. receptors, enzymes, enzyme substrates, prior to or in addition to the fluorescent probe. Preferred cell lines include but are not limited to those of fibroblast origin, e.g. BHK, CHO, BALB, or of endothelial origin, e.g. HUVEC, BAE (bovine artery endothelial), CPAE (cow pulmonary artery endothelial) or of pancreatic origin, e.g. RIN, INS-1, MIN6, bTC3, aTC6, bTC6, HIT, or of hematopoietic origin, e.g. adipocyte origin, e.g. 3T3-L1, neuronal/neuroendocrine origin, e.g. AtT20, PC12, GH3, muscle origin, e.g. SKMC, A10, C2C12, renal origin, e.g. HEK 293, LLC-PK1.

The term "hybrid polypeptide" is intended to indicate a polypeptide which is a fusion of at least a portion of each of two proteins, in this case at least a portion of the green fluorescent protein, and at least a portion of a catalytic and/or regulatory domain of a protein kinase. Furthermore a hybrid polypeptide is intended to indicate a fusion polypeptide comprising a

20

25

30

GFP or at least a portion of the green fluorescent protein that contains a functional fluorophore, and at least a portion of a biologically active polypeptide as defined herein provided that said fusion is not the PKC $\alpha$ -GFP, PKC $\gamma$ -GFP, and PKC $\epsilon$ -GFP disclosed by Schmidt et al. and Sakai et al., respectively. Thus, GFP may be N- or C-terminally tagged to a biologically active polypeptide, optionally via a linker portion or linker peptide consisting of a sequence of one or more amino acids. The hybrid polypeptide or fusion polypeptide may act as a fluorescent probe in intact living cells carrying a DNA sequence encoding the hybrid polypeptide under conditions permitting expression of said hybrid polypeptide.

The term "kinase" is intended to indicate an enzyme that is capable of phosphorylating a cellular component.

The term "protein kinase" is intended to indicate an enzyme that is capable of phosphorylating serine and/or threonine and/or tyrosine in peptides and/or proteins.

The term "phosphatase" is intended to indicate an enzyme that is capable of dephosphorylating phosphoserine and/or phosphothreonine and/or phosphotyrosine in peptides and/or proteins.

In the present context, the term "biologically active polypeptide" is intended to indicate a polypeptide affecting intracellular processes upon activation, such as an enzyme which is active in intracellular processes or a portion thereof comprising a desired amino acid sequence which has a biological function or exerts a biological effect in a cellular system. In the polypeptide one or several aminoacids may have been deleted, inserted or replaced to alter its biological function, e.g. by rendering a catalytic site inactive. Preferably, the biologically active polypeptide is selected from the group consisting of proteins taking part in an intracellular signalling pathway, such as enzymes involved in the intracellular phosphorylation and dephosphorylation processes including kinases, protein kinases and phosphorylases as defined herein, but also proteins making up the cytoskeleton play important roles in intracellular signal transduction and are therefore included in the meaning of "biologically active polypeptide" herein. More preferably, the biologically active polypeptide is a protein which according to its state as activated or non-activated changes localisation within the cell, preferably as an in-

termediary component in a signal transduction pathway. Included in this preferred group of biologically active polypeptides are cAMP dependent protein kinase A.

The term "a substance having biological activity" is intended to indicate any sample which has a biological function or exerts a biological effect in a cellular system. The sample may be a sample of a biological material such as a sample of a body fluid including blood, plasma, saliva, milk, urine, or a microbial or plant extract, an environmental sample containing pollutants including heavy metals or toxins, or it may be a sample containing a compound or mixture of compounds prepared by organic synthesis or genetic techniques.

10

15

20

The phrase "any change in fluorescence" means any change in absorption properties, such as wavelength and intensity, or any change in spectral properties of the emitted light, such as a change of wavelength, fluorescence lifetime, intensity or polarisation, or any change in the intracellular localisation of the fluorophore. It may thus be localised to a specific cellular component (e.g. organelle, membrane, cytoskeleton, molecular structure) or it may be evenly distributed throughout the cell or parts of the cell.

The phrase "back-tracking of a signal transduction pathway" is intended to indicate.

The term "organism" as used herein indicates any unicellular or multicellular organism preferably originating from the animal kingdom including protozoans, but also organisms that are members of the plant kingdoms, such as algae, fungi, bryophytes, and vascular plants are included in this definition.

The term "nucleic acid" is intended to indicate any type of poly- or oligonucleic acid sequence, such as a DNA sequence, a cDNA sequence, or an RNA sequence.

25

30

The term "biologically equivalent" as it relates to proteins is intended to mean that a first protein is equivalent to a second protein if the cellular functions of the two proteins may substitute for each other, e.g. if the two proteins are closely related isoforms encoded by different genes, if they are splicing variants, or allelic variants derived from the same gene, if they perform identical cellular functions in different cell types, or in different species. The term "biologically equivalent" as it relates to DNA is intended to mean that a first DNA sequ-

ence encoding a polypeptide is equivalent to a second DNA sequence encoding a polypeptide if the functional proteins encoded by the two genes are biologically equivalent.

The phrase "back-tracking of a signal transduction pathway" is intended to indicate a process for defining more precisely at what level a signal transduction pathway is affected, either by the influence of chemical compounds or a disease state in an organism. Consider a specific signal transduction pathway represented by the bioactive polypeptides A - B - C - D, with signal transduction from A towards D. When investigating all components of this signal transduction pathway compounds or disease states that influence the activity or redistribution of only D can be considered to act on C or downstream of C whereas compounds or disease states that influence the activity or redistribution of C and D, but not of A and B can be considered to act downstream of B.

The term "fixed cells" is used to mean cells treated with a cytological fixative such as glutaraldehyde or formaldehyde, treatments which serve to chemically cross-link and stabilize soluble and insoluble proteins within the structure of the cell. Once in this state, such proteins cannot be lost from the structure of the now-dead cell.

20

25

15

. 10

# **BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1. CHO cells expressing the PKAc-F64L-S65T-GFP hybrid protein have been treated in HAM's F12 medium with 50 mM forskolin at 37°C. The images of the GFP fluorescence in these cells have been taken at different time intervals after treatment, which were: a) 40 seconds b) 60 seconds c) 70 seconds d) 80 seconds. The fluorescence changes from a punctate to a more even distribution within the (non-nuclear) cytoplasm.

10

15

20

25

30

Figure 2. Time-lapse analysis of forskolin induced PKAc-F64L-S65T-GFP redistribution. CHO cells, expressing the PKAc-F64L-S65T-GFP fusion protein were analysed by time-lapse fluorescence microscopy. Fluorescence micrographs were acquired at regular intervals from 2 min before to 8 min after the addition of agonist. The cells were challenged with 1 mM forskolin immediately after the upper left image was acquired (t=0). Frames were collected at the following times: i) 0, ii) 1, iii) 2, iv) 3, v) 4 and vi) 5 minutes. Scale bar 10 mm.

Figure 3. Time-lapse analyses of PKAc-F64L-S65T-GFP redistribution in response to various agonists. The effects of 1 mM forskolin (A), 50 mM forskolin (B), 1 mM dbcAMP (C) and 100 mM IBMX (D) (additions indicated by open arrows) on the localisation of the PKAc-F64L-S65T-GFP fusion protein were analysed by time-lapse fluorescence microscopy of CHO/PKAc-F64L-S65T-GFP cells. The effect of addition of 10 mM forskolin (open arrow), followed shortly by repeated washing with buffer (solid arrow), on the localisation of the PKAc-F64L-S65T-GFP fusion protein was analysed in the same cells (E). In a parallel experiment, the effect of adding 10 mM forskolin and 100 mM IBMX (open arrow) followed by repeated washing with buffer containing 100 mM IBMX (solid arrow) was analysed (F). Removing forskolin caused PKAc-F64L-S65T-GFP fusion protein to return to the cytoplasmic aggregates while this is prevented by the continued presence of IBMX (F). The effect of 100 nM glucagon (Fig 3G, open arrow) on the localisation of the PKAc-F64L-S65T-GFP fusion protein is also shown for BHK/GR, PKAc-F64L-S65T-GFP cells. The effect of 10 mM norepinephrine (H), solid arrow, on the localisation of the PKAc-F64L-S65T-GFP fusion protein was analysed similarly, in transiently transfected CHO, PKAc-F64L-S65T-GFP cells, pretreated with 10 mM forskolin, open arrow, to increase [cAMP], N.B. in Fig 3H the x-axis counts the image numbers, with 12 seconds between images. The raw data of each experiment consisted of 60 fluorescence micrographs acquired at regular intervals including several images acquired before the addition of buffer or agonist. The charts (A-G) each show a quantification of the response seen through all the 60 images, performed as described in analysis method 2. The change in total area of the highly fluorescent aggregates, relative to the initial area of fluorescent aggregates is plotted as the ordinate in all graphs in Figure 3, versus time for each experiment. Scale bar 10 mm.

Figure 4. Dose response curve (two experiments) for forskolin-induced redistribution of the PKAc-F64L-S65T-GFP fusion.

5

10

Figure 5. Time from initiation of a response to half maximal ( $t_{1/2\text{max}}$ ) and maximal ( $t_{\text{max}}$ ) PKAc-F64L-S65T-GFP redistribution. The data was extracted from curves such as that shown in "Figure 2." All  $t_{1/2\text{max}}$  and  $t_{\text{max}}$  values are given as mean±SD and are based on a total of 26-30 cells from 2-3 independent experiments for each forskolin concentration. Since the observed redistribution is sustained over time, the  $t_{\text{max}}$  values were taken as the earliest time point at which complete redistribution is reached. Note that the values do not relate to the degree of redistribution.

15

Figure 6. Parallel dose response analyses of forskolin induced cAMP elevation and PKAc-F64L-S65T-GFP redistribution. The effects of buffer or 5 increasing concentrations of forskolin on the localisation of the PKAc-F64L-S65T-GFP fusion protein in CHO/PKAc-F64L-S65T-GFP cells, grown in a 96 well plate, were analysed as described above. Computing the ratio of the SD's of fluorescence micrographs taken of the same field of cells, prior to and 30 min after the addition of forskolin, gave a reproducible measure of PKAc-F64L-S65T-GFP redistribution. The graph shows the individual 48 measurements and a trace of their mean±s.e.m at each forskolin concentration. For comparison, the effects of buffer or 8 increasing concentrations of forskolin on [cAMP], was analysed by a scintillation proximity assay of cells grown under the same conditions. The graph shows a trace of the mean ± s.e.m of 4 experiments expressed in arbitrary units.

25

30

20

Figure 7. BHK cells stably transfected with the human muscarinic (hM1) receptor and the PKCa-F64L-S65T-GFP fusion. Carbachol (100 mM added at 1.0 second) induced a transient redistribution of PKCa-F64L-S65T-GFP from the cytoplasm to the plasma membrane. Images were taken at the following times: a) 1 second before carbachol addition, b) 8.8 seconds after addition and c) 52.8 seconds after addition.

WO 98/45704 PCT/DK98/00145

Figure 8. BHK cells stably transfected with the hM1 receptor and PKCa-F64L-S65T-GFP fusion were treated with carbachol (1 mM, 10 mM, 100 mM). In single cells intracellular [Ca²+] was monitored simultaneously with the redistribution of PKCa-F64L-S65T-GFP. Dashed line indicates the addition times of carbachol. The top panel shows changes in the intracellular Ca²+ concentration of individual cells with time for each treatment. The middle panel shows changes in the average cytoplasmic GFP fluorescence for individual cells against time for each treatment. The bottom panel shows changes in the fluorescence of the periphery of single cells, within regions that specifically include the circumferential edge of a cell as seen in normal projection, the regions which offers best chance to monitor changes in the fluorescence intensity of the plasma membrane.

- Figure 9. a) The hERK1-F64L-S65T-GFP fusion expressed in HEK293 cells treated with 100 mM of the MEK1 inhibitor PD98059 in HAM F-12 (without serum) for 30 minutes at 37 °C. The nuclei empty of fluorescence during this treatment.
- b) The same cells as in (a) following treatment with 10 % foetal calf serum for 15 minutes at 37 °C.
- c) Time profiles for the redistribution of GFP fluorescence in HEK293 cells following treatment with various concentrations of EGF in Hepes buffer (HAM F-12 replaced with Hepes buffer directly before the experiment). Redistribution of fluorescence is expressed as the change in the ratio value between areas in nucleus and cytoplasm of single cells. Each time profile is the mean for the changes seen in six single cells.
- d) Bar chart for the end-point measurements, 600 seconds after start of EGF treatments, of fluorescence change (nucleus:cytoplasm) following various concentrations of EGF.

25

10

15

20

Figure 10.

- a) The SMAD2-EGFP fusion expressed in HEK293 cells starved of serum overnight in HAM F-12. HAM F-12 was then replaced with Hepes buffer pH 7.2 immediately before the experiment. Scale bar is 10 mm.
- b) HEK 293 cells expressing the SMAD2-EGFP fusion were treated with various concentration of TGF-beta as indicated, and the redistribution of fluorescence monitored against time.

WO 98/45704 PCT/DK98/00145

29

The time profile plots represent increases in fluorescence within the nucleus, normalised to starting values in each cell measured. Each trace is the time profile for a single cell nucleus.

c) A bar chart representing the end-point change in fluorescence within nuclei (after 850 seconds of treatment) for different concentrations of TGF-beta. Each bar is the value for a single nucleus in each treatment.

Figure 11. The VASP-F64L-S65T-GFP fusion in CHO cells stably transfected with the human insulin receptor. The cells were starved for two hours in HAM F-12 without serum, then treated with 10% foetal calf serum. The image shows the resulting redistribution of fluorescence after 15 minutes of treatment. GFP fluorescence becomes localised in structures identified as focal adhesions along the length of actin stress fibres.

Figure 12. Time lapse recording GLUT4-GFP redistribution in CHO-HIR cells. Time indicates minutes after the addition of 100 nM insulin.

15

10

### **EXAMPLE 1**

Construction, testing and implementation of an assay for cAMP based on PKA activation in real time within living cells.

Useful for monitoring the activity of signalling pathways which lead to altered concentrations of cAMP, e.g. activation of G-protein coupled receptors which couple to G-proteins of the G<sub>s</sub> or G<sub>i</sub> class.

10

20

The catalytic subunit of the murine cAMP dependent protein kinase (PKAc)was fused C-terminally to a F64L-S65T derivative of GFP. The resulting fusion (PKAc-F64L-S65T-GFP) was used for monitoring *in vivo* the translocation and thereby the activation of PKA.

Construction of the PKAc-F64L-S65T-GFP fusion:

15 Convenient restriction endonuclease sites were introduced into the cDNAs encoding murine PKAc (Gen Bank Accession number: M12303) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) by polymerase chain reaction (PCR). The PCR reactions were performed according to standard protocols with the following primers:

5'PKAc: TTggACACAAgCTTTggACACCCTCAggATATgggCAACgCCgCCgCCGCCAAg (SEQ ID NO:3),

3'PKAc: gTCATCTTCTCgAgTCTTTCAggCgCgCCCAAACTCAgTAAACTCCTTgCCACAC (SEQ ID NO:4),

5'GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAACTTTTC (SEQ ID NO:1),

25 3'GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgCCATgT (SEQ ID NO:2).

10

15

30

The PKAc amplification product was then digested with HindIII+AscI and the F64L-S65T-GFP product with AscI+XhoI. The two digested PCR products were subsequently ligated with a HindIII+XhoI digested plasmid (pZeoSV® mammalian expression vector, Invitrogen, San Diego, CA, USA). The resulting fusion construct (SEQ ID NO:68 & 69) was under control of the SV40 promoter.

Transfection and cell culture conditions.

Chinese hamster ovary cells (CHO), were transfected with the plasmid containing the PKAc-F64L-S65T-GFP fusion using the calcium phosphate precipitate method in HEPES-buffered saline (Sambrook *et al.*, 1989). Stable transfectants were selected using 1000 mg Zeocin/ml (Invitrogen) in the growth medium (DMEM with 1000 mg glucose/l, 10 % fetal bovine serum (FBS), 100 mg penicillin-streptomycin mixture ml<sup>-1</sup>, 2 mM L-glutamine purchased from Life Technologies Inc., Gaithersburg, MD, USA). Untransfected CHO cells were used as the control. To assess the effect of glucagon on fusion protein translocation, the PKAc-F64L-S65T-GFP fusion was stably expressed in baby hamster kidney cells overexpressing the human glucagon receptor (BHK/GR cells) Untransfected BHK/GR cells were used as the control. Expression of GR was maintained with 500 mg G418/ml (*Neo* marker) and PKAc-F64L-S65T-GFP was maintained with 500 mg Zeocin/ml (*Sh ble* marker). CHO cells were also simultaneously co-transfected with vectors containing the PKAc-F64L-S65T-GFP fusion and the human a2a adrenoceptor (hARa2a).

For fluorescence microscopy, cells were allowed to adhere to Lab-Tek chambered coverglasses (Nalge Nunc Int., Naperville, IL, USA) for at least 24 hours and cultured to about 80% confluence. Prior to experiments, the cells were cultured over night without selection pressure in HAM F-12 medium with glutamax (Life Technologies), 100 mg penicillinstreptomycin mixture ml<sup>-1</sup> and 0.3 % FBS. This medium has low autofluorescence enabling fluorescence microscopy of cells straight from the incubator.

Monitoring activity of PKA activity in real time:

Image aquisition of live cells were gathered using a Zeiss Axiovert 135M fluorescence microscope fitted with a Fluar 40X, NA: 1.3 oil immersion objective and coupled to a Photometrics CH250 charged coupled device (CCD) camera. The cells were illuminated with a 100 W HBO arc lamp. In the light path was a 470±20 nm excitation filter, a 510 nm dichroic mirror

15

and a 515±15 nm emission filter for minimal image background. The cells were kept and monitored to be at 37°C with a custom built stage heater.

Images were processed and analyzed in the following manner:.

Method 1: Stepwise procedure for quantitation of translocation of PKA:

- 1. The image was corrected for dark current by performing a pixel-by-pixel subtraction of a dark image (an image taken under the same conditions as the actual image, except the camera shutter is not allowed to open).
  - 2. The image was corrected for non-uniformity of the illumination by performing a pixel-bypixel ratio with a flat field correction image (an image taken under the same conditions as the actual image of a uniformly fluorescent specimen).
  - 3. The image histogram, i.e., the frequency of occurrence of each intensity value in the image, was calculated.
  - 4. A smoothed, second derivative of the histogram was calculated and the second zero is determined. This zero corresponds to the inflection point of the histogram on the high side of the main peak representing the bulk of the image pixel values.
  - 5. The value determined in step 4 was subtracted from the image. All negative values were discarded.
  - 6. The variance (square of the standard deviation) of the remaining pixel values was determined. This value represents the "response" for that image.
- 20 7. Scintillation proximity assay (SPA) for independent quantitation of cAMP:

# Method 2: Alternative method for quantitation of PKA redistribution:

- 1. The fluorescent aggregates are segmented from each image using an automatically found threshold based on the maximisation of the information measure between the object and background. The *a priori* entropy of the image histogram is used as the information measure.
  - 2. The area of each image occupied by the aggregates is calculated by counting pixels in the segmented areas.
- 3. The value obtained in step 2 for each image in a series, or treatment pair, is normalised to the value found for the first (unstimulated) image collected. A value of zero (0) indicates no redistribution of fluorescence from the starting condition. A value of one (1) by this method equals full redistribution.
- 15 Cells were cultured in HAM F-12 medium as described above, but in 96-well plates. The medium was exchanged with Ca<sup>2+</sup>-HEPES buffer including 100 mM IBMX and the cells were stimulated with different concentrations of forskolin for 10 min. Reactions were stopped with addition of NaOH to 0.14 M and the amount of cAMP produced was measured with the cAMP-SPA kit. RPA538 (Amersham) as described by the manufacturer.

20

Manipulating intracellular levels of cAMP to test the PKAc-F64L-S65T-GFP fusion.

The following compounds were used to vary cAMP levels: Forskolin, an activator of adenylate cyclase; dbcAMP, a membrane permeable cAMP analog which is not degraded by phosphodiesterase; IBMX, an inhibitor of phosphodiesterase.

- 25 CHO cells stably expressing the PKAc-F64L-S65T-GFP, showed a dramatic translocation of the fusion protein from a punctate distribution to an even distribution throughout the cytoplasm following stimulation with 1 mM forskolin (n=3), 10 mM forskolin (n=4) and 50 mM forskolin (n=4) (Fig 1), or dbcAMP at 1mM (n=6).
  - Fig. 2 shows the progression of response in time following treatment with 1 mM forskolin.

20

30

Fig. 3 gives a comparison of the average temporal profiles of fusion protein redistribution and a measure of the extent of each response to the three forskolin concentrations (Fig. 3A, E, B), and to 1 mM dbcAMP (fig 3C) which caused a similar but slower response, and to addition of 100 mM IBMX (n=4, Fig. 3D) which also caused a slow response, even in the absence of adenylate cyclase stimulation. Addition of buffer (n=2) had no effect (data not shown).

As a control for the behavior of the fusion protein, F64L-S65T-GFP alone was expressed in CHO cells and these were also given 50 mM forskolin (n=5); the uniform diffuse distribution characteristic of GFP in these cells was unaffected by such treatment (data not shown).

The forskolin induced translocation of PKAc-F64L-S65T-GFP showed a dose-response relationship (Fig 4 and 6), see quantitative procedures above.

Reversibility of PKAc-F64L-S65T-GFP translocation.

The release of the PKAc probe from its cytoplasmic anchoring hotspots was reversible. Washing the cells repeatedly (5-8 times) with buffer after 10µM forskolin treatment completely restored the punctate pattern within 2-5 min (n=2, Fig. 3E). In fact the fusion protein returned to a pattern of fluorescent cytoplasmic aggregates virtually indistinguishable from that observed before forskolin stimulation.

To test whether the return of fusion protein to the cytoplasmic aggregates reflected a decreased [cAMP], cells were treated with a combination of 10 mM forskolin and 100 mM IBMX (n=2) then washed repeatedly (5-8 times) with buffer containing 100 mM IBMX (Fig. 3F). In these experiments, the fusion protein did not return to its prestimulatory localization after removal of forskolin.

25 Testing the PKA-F64L-S65T-GFP probe with physiologically relevant agents.

To test the probe's response to receptor activation of adenylate cyclase, BHK cells stably transfected with the glucagon receptor and the PKA-F64L-S65T-GFP probe were exposed to glucagon stimulation. The glucagon receptor is coupled to a G<sub>s</sub> protein which activates adenylate cyclase, thereby increasing the cAMP level. In these cells, addition of 100 nM glucagon (n=2) caused the release of the PKA-F64L-S65T-GFP probe from the cytoplasmic aggregates and a resulting translocation of the fusion protein to a more even cytoplasmic

distribution within 2-3 min (Fig. 3G). Similar but less pronounced effects were seen at lower glucagon concentrations (n=2, data not shown). Addition of buffer (n=2) had no effect over time (data not shown).

Transiently transfected CHO cells expressing hARa2a and the PKA-F64L-S65T-GFP probe were treated with 10 mM forskolin for 7.5 minutes, then, in the continued presence of forskolin, exposed to 10 mM norepinephrine to stimulate the exogenous adrenoreceptors, which couple to a G<sub>I</sub> protein, which inhibit adenylate cyclase. This treatment led to reappearance of fluorescence in the cytoplasmic aggregates indicative of a decrease in [cAMP]<sub>I</sub> (Fig. 3H).

10

15

20

25

Fusion protein translocation correlated with [cAMP],

As described above, the time it took for a response to come to completion was dependent on the forskolin dose (Fig. 5) In addition the degree of responses was also dose dependent. To test the PKA-F64L-S65T-GFP fusion protein translocation in a semi high through-put system, CHO cells stably transfected with the PKA-F64L-S65T-GFP fusion was stimulated with buffer and 5 increasing doses of forskolin (n=8). Using the image analysis algorithm described above (Method 1), a dose response relationship was observed in the range from 0.01-50 mM forskolin (Fig. 6). A half maximal stimulation was observed at about 2 mM forskolin. In parallel, cells were stimulated with buffer and 8 increasing concentrations of forskolin (n=4) in the range 0.01-50 mM. The amount of cAMP produced was measured in an SPA assay. A steep increase was observed between 1 and 5 mM forskolin coincident with the steepest part of the curve for fusion protein translocation (also Fig. 6)

# **EXAMPLE 2**

Quantitation of redistribution in real-time within living cells.

Probe for detection of PKC activity in real time within living cells:

Construction of PKC-GFP fusion:

The probe was constructed by ligating two restriction enzyme treated polymerase chain reaction (PCR) amplification products of the cDNA for murine PKCα (GenBank Accession number: M25811) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) respectively. Tag® polymerase and the following oligonucleotide primers were used for PCR;

5 5'mPKCa: TTggACACAAgCTTTggACACCCTCAggATATggCTgACgTTTACCCggCCAACg (SEQ ID NO:5),

3'mPKCa: gTCATCTTCTCgAgTCTTTCAggCgCgCCCTACTgCACTTTgCAAgATTgggTgC (SEQ ID NO:6),

5'F64L-S65T-GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAAGAACTT-TTC (SEQ ID NO:1),

3'F64L-S65T-GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgC-CATgT (SEQ ID NO:2).

The hybrid DNA strand was inserted into the pZeoSV® mammalian expression vector as a HindIII-Xhol casette as described in example 1.

#### 15 Cell Culture:

10

20

25

BHK cells expressing the human M1 receptor under the control of the inducible metal-lothionine promoter and maintained with the dihydrofolate reductase marker were transfected with the PKCα-F64L-S65T-GFP probe using the calcium phosphate precipitate method in HEPES buffered saline (HBS [pH 7.10]). Stable transfectants were selected using 1000 μg Zeocin®/ml in the growth medium (DMEM with 1000 mg glucose/l, 10 % foetal bovine serum (FBS), 100 mg penicillin-streptomycin mixture ml-1, 2 mM l-glutamine). The hM1 receptor and PKCα-F64L-S65T-GFP fusion protein were maintained with 500 nM methotrexate and 500 μg Zeocin®/ml respectively. 24 hours prior to any experiment, the cells were transferred to HAM F-12 medium with glutamax, 100 μg penicillin-streptomycin mixture ml¹ and 0.3 % FBS. This medium relieves selection pressure, gives a low induction of signal transduction pathways and has a low autofluorescence at the relevant wavelength enabling fluorescence microscopy of cells straight from the incubator.

Monitoring the PKC activity in real time:

Digital images of live cells were gathered using a Zeiss Axiovert 135M fluorescence microscope fitted with a 40X, NA: 1.3 oil immersion objective and coupled to a Photometrics

20

25

CH250 charged coupled device (CCD) camera. The cells were illuminated with a 100 W arc lamp. In the light path was a 470±20 nm excitation filter, a 510 nm dichroic mirror and a 515±15 nm emission filter for minimal image background. The cells were kept and monitored to be at 37°C with a custom built stage heater.

5 Images were analyzed using the IPLab software package for Macintosh.

Upon stimulation of the M1-BHK cells, stably expressing the PKCα-F64L-S65T-GFP fusion, with carbachol we observed a dose-dependent transient translocation from the cytoplasm to the plasma membrane (Fig. 7a,b,c). Simultaneous measurement of the cytosolic free calcium concentration shows that the carbachol-induced calcium mobilisation precedes the translocation (Fig. 8).

Stepwise procedure for quantitation of translocation of PKC:

- 1. The image was corrected for dark current by performing a pixel-by-pixel subtraction of a dark image (an image taken under the same conditions as the actual image, except the camera shutter is not allowed to open).
- 15 2. The image was corrected for non-uniformity of the illumination by performing a pixel-bypixel ratio with a flat field correction image (an image taken under the same conditions as the actual image of a uniformly fluorescent specimen).
  - 3. A copy of the image was made in which the edges are identified. The edges in the image are found by a standard edge-detection procedure convolving the image with a kernel which removes any large-scale unchanging components (i.e., background) and accentuates any small-scale changes (i.e., sharp edges). This image was then converted to a binary image by threshholding. Objects in the binary image which are too small to represent the edges of cells were discarded. A dilation of the binary image was performed to close any gaps in the image edges. Any edge objects in the image which were in contact with the borders of the image are discarded. This binary image represents the edge mask.
    - 4. Another copy of image was made via the procedure in step 3. This copy was further processed to detect objects which enclose "holes" and setting all pixels inside the holes to the binary value of the edge, i.e., one. This image represents the whole cell mask.
- The original image was masked with the edge mask from step 3 and the sum total of all
   pixel values is determined.

- 6. The original image was masked with the whole cell mask from step 4 and the sum total of all pixel values was determined.
- 7. The value from step 5 was divided by the value from step 6 to give the final result, the fraction of fluorescence intensity in the cells which was localized in the edges.

# **EXAMPLE 3**

Probes for detection of mitogen activated protein kinase Erk1 redistribution.

Useful for monitoring signalling pathways involving MAPK, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Erk1, a serine/threonine protein kinase, is a component of a signalling pathway which is activated by e.g. many growth factors.

Probes for detection of ERK-1 activity in real time within living cells:

- The extracellular signal regulated kinase (ERK-1, a mitogen activated protein kinase, MAPK) is fused N- or C-terminally to a derivative of GFP. The resulting fusions expressed in different mammalian cells are used for monitoring *in vivo* the nuclear translocation, and thereby the activation, of ERK1 in response to stimuli that activate the MAPK pathway.
  - a) Construction of murine ERK1 F64L-S65T-GFP fusion:
- Convenient restriction endonuclease sites are introduced into the cDNAs encoding murine ERK1 (GenBank Accession number: Z14249) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) by polymerase chain reaction (PCR). The PCR reactions are performed according to standard protocols with the following primers:
- 5'ERK1: TTggACACAAgCTTTggACACCCTCAggATATggCggCggCggCggCggCTCCgggggggCgggg (SEQ ID NO:7),

25

30

5'F64L-S65T-GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAAGAACTT-TTC (SEQ ID NO:1)

5 3'F64L-S65T-GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgC-CATgT (SEQ ID NO:2)

To generate the mERK1-F64L-S65T-GFP (SEQ ID NO:56 & 57) fusion the ERK1 amplification product is digested with HindIII+AscI and the F64L-S65T-GFP product with AscI+Xhol. To generate the F64L-S65T-GFP-mERK1 fusion the ERK1 amplification product is then digested with HindIII+Bsu36I and the F64L-S65T-GFP product with Bsu36I+Xhol. The two pairs of digested PCR products are subsequently ligated with a HindIII+Xhol digested plasmid (pZeoSV® mammalian expression vector, Invitrogen, San Diego, CA, USA). The resulting fusion constructs are under control of the SV40 promoter.

b) The human Erk1 gene (GenBank Accession number: X60188) was amplified using PCR according to standard protocols with primers Erk1-top (SEQ ID NO:9) and Erk1-bottom/+stop (SEQ ID NO:10). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Erk1 fusion (SEQ ID NO:38 &39) under the control of a CMV promoter.

The plasmid containing the EGFP-Erk1 fusion was transfected into HEK293 cells employing the FUGENE transfection reagent (Boehringer Mannheim). Prior to experiments the cells were grown to 80%-90% confluency 8 well chambers in DMEM with 10% FCS. The cells were washed in plain HAM F-12 medium (without FCS), and then incubated for 30-60 minutes in plain HAM F-12 (without FCS) with 100 micromolar PD98059, an inhibitor of MEK1, a kinase which activates Erk1; this step effectively empties the nucleus of EGFP-Erk1. Just before starting the experiment, the HAM F-12 was replaced with Hepes buffer following a wash with Hepes buffer. This removes the PD98059 inhibitor; if blocking of MEK1 is still wanted (e.g. in control experiments), the inhibitor is included in the Hepes buffer.

The experimental setup of the microscope was as described in example 1.

60 images were collected with 10 seconds between each, and with the test compound added after image number 10.

Addition of EGF (1-100 nM) caused within minutes a redistribution of EGFP-Erk1 from the cytoplasm into the nucleus (Fig. 9a,b).

The response was quantitated as described below and a dose-dependent relationship between EGF concentration and nuclear translocation of EGFP-Erk1 was found (Fig. 9c,d). Reditribution of GFP fluorescence is expressed in this example as the change in the ratio value between areas in nuclear versus cytoplasmic compartments of the cell. Each time profile is the average of nuclear to cytoplasmic ratios from six cells in each treatment.

#### **EXAMPLE 4:**

10

15

Probes for detection of Erk2 redistribution.

Useful for monitoring signalling pathways involving MAPK, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Erk2, a serine/threonine protein kinase, is closely related to Erk1 but not identical; it is a component of a signalling pathway which is activated by e.g. many growth factors.

- a) The rat Erk2 gene (GenBank Accession number: M64300) was amplified using PCR according to standard protocols with primers Erk2-top (SEQ ID NO:11) and Erk2-bottom/+stop (SEQ ID NO:13) The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-Erk2 fusion (SEQ ID NO:40 &41) under the control of a CMV promoter.
- b) The rat Erk2 gene (GenBank Accession number: M64300) was amplified using PCR according to standard protocols with primers (SEQ ID NO:11) Erk2-top and Erk2-bottom/-stop (SEQ ID NO:12). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces an Erk2-EGFP fusion (SEQ ID NO:58 &59) under the control of a CMV promoter.

The resulting plasmids were transfected into CHO cells and BHK cells. The cells were grown under standard conditions. Prior to experiments, the cells were starved in medium without serum for 48-72 hours. This led to a predominantly cytoplasmic localization of both probes, especially in BHK cells. 10% fetal calf serum was added to the cells and the fluorescence of the cells was recorded as explained in example 3. Addition of serum caused the probes to redistribute into the nucleus within minutes of addition of serum.

#### **EXAMPLE 5:**

15

20

25

10 Probes for detection of Smad2 redistribution.

Useful for monitoring signalling pathways activated by some members of the transforming growth factor-beta family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Smad 2, a signal transducer, is a component of a signalling pathway which is induced by some members of the TGFbeta family of cytokines.

- a) The human Smad2 gene (GenBank Accession number: AF027964) was amplified using PCR according to standard protocols with primers Smad2-top (SEQ ID NO:24) and Smad2-bottom/+stop (SEQ ID NO:26). The PCR product was digested with restriction enzymes E-coR1 and Acc65I, and ligated into pEGFP-C1 (Clontech; Palo Alto; GenBank Accession number U55763) digested with EcoR1 and Acc65I. This produces an EGFP-Smad2 fusion (SEQ ID NO:50&51) under the control of a CMV promoter.
- b) The human Smad2 gene (GenBank Accession number: AF027964) was amplified using PCR according to standard protocols with primers Smad2-top (SEQ ID NO:24) and Smad2-bottom/-stop (SEQ ID NO:25). The PCR product was digested with restriction enzymes E-coR1 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and Acc65I. This produces a Smad2-EGFP fusion (SEQ ID NO:74 &75) under the control of a CMV promoter.
- The plasmid containing the EGFP-Smad2 fusion was transfected into HEK293 cells, where it showed a cytoplasmic distribution. Prior to experiments the cells were grown in 8 well Nunc

chambers in DMEM with 10% FCS to 80% confluency and starved overnight in HAM F-12 medium without FCS.

For experiments, the HAM F-12 medium was replaced with Hepes buffer pH 7.2.

The experimental setup of the microscope was as described in example 1.

5 90 images were collected with 10 seconds between each, and with the test compound added after image number 5.

After serum starvation of cells, each nucleus contains less GFP fluorescence than the surrounding cytoplasm (Fig. 10a). Addition of TGFbeta caused within minutes a redistribution of EGFP-Smad2 from the cytoplasma into the nucleus (Fig. 10b).

The redistribution of fluorescence within the treated cells was quantified simply as the fractional increase in nuclear fluorescence normalised to the starting value of GFP fluorescence in the nucleus of each unstimulated cell.

# 15 EXAMPLE 6:

10

20

25

Probe for detection of VASP redistribution.

Useful for monitoring signalling pathways involving rearrangement of cytoskeletal elements, e.g. to identify compounds which modulate the activity of the pathway in living cells.

VASP, a phosphoprotein, is a component of cytoskeletal structures, which redistributes in response to signals which affect focal adhesions.

a) The human VASP gene (GenBank Accession number: Z46389) was amplified using PCR according to standard protocols with primers VASP-top (SEQ ID NO:94) and VASP-bottom/+stop (SEQ ID NO:95). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Hind3and BamH1. This produces an EGFP-VASP fusion (SEQ ID NO:124 &125) under the control of a CMV promoter.

The resulting plasmid was transfected into CHO cells expressing the human insulin receptor using the calcium-phosphate transfection method. Prior to experiments, cells were grown in 8 well Nunc chambers and starved overnight in medium without FCS.

Experiments are performed in a microscope setup as described in example 1.

10% FCS was added to the cells and images were collected. The EGFP-VASP fusion was redistributed from a somewhat even distribution near the periphery into more localized structures, identified as focal adhesion points (Fig. 11).

5

A large number of further GFP fusions have been made or are in the process of being made, as apparent from the following Examples 7-22 which also suggest suitable host cells and substances for activation of the cellular signalling pathways to be monitored and analyzed.

10

### **EXAMPLE 7:**

Probe for detection of actin redistribution.

Useful for monitoring signalling pathways involving rearrangement or formation of actin filaments, e.g. to identify compounds which modulate the activity of pathways leading to cytoskeletal rearrangements in living cells.

Actin is a component of cytoskeletal structures, which redistributes in response to very many cellular signals.

20

25

30

The actin binding domain of the human alpha-actinin gene (GenBank Accession number: X15804) was amplified using PCR according to standard protocols with primers ABD-top (SEQ ID NO:90) and ABD-bottom/-stop (SEQ ID NO:91). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Hind3 and BamH1. This produced an actin-binding-domain-EGFP fusion (SEQ ID NO:128 &129) under the control of a CMV promoter.

The resulting plasmid was transfected into CHO cells expressing the human insulin receptor. Cells were stimulated with insulin which caused the actin binding domain-EGFP probe to become redistributed into morphologically distinct membrane-associated structures.

### Example 8:

10

20

Probes for detection of p38 redistribution.

- Useful for monitoring signalling pathways responding to various cellular stress situations, e.g. to identify compounds which modulate the activity of the pathway in living cells, or as a counterscreen.
  - p38, a serine/thronine protein kinase, is a component of a stress-induced signalling pathway which is activated by many types of cellular stress, e.g. TNFalpha, anisomycin, UV and mitomycin C.
- a) The human p38 gene (GenBank Accession number: L35253) was amplified using PCR according to standard protocols with primers p38-top (SEQ ID NO:14) and p38-bottom/+stop (SEQ ID NO: 16). The PCR product was digested with restriction enzymes
   Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produced an EGFP-p38 fusion (SEQ ID NO:46 &47) under the control of a CMV promoter.
  - b) The human p38 gene (GenBank Accession number: L35253) was amplified using PCR according to standard protocols with primers p38-top (SEQ ID NO:13) and p38-bottom/-stop (SEQ ID NO:15). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a p38-EGFP fusion (SEQ ID NO:64 &65) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. HEK293, in which the EGFP-p38 probe and/or the p38-EGFP probe should change its cellular distribution from predominantly cytoplasmic to nuclear within minutes in response to activation of the signal-ling pathway with e.g. anisomycin.

#### Example 9:

30 Probes for detection of Jnk1 redistribution.

Useful for monitoring signalling pathways responding to various cellular stress situations, e.g. to identify compounds which modulate the activity of the pathway in living cells, or as a counterscreen.

Jnk1, a serine/threonine protein kinase, is a component of a stress-induced signalling pathway different from the p38 described above, though it also is activated by many types of cellular stress, e.g. TNFalpha, anisomycin and UV.

- a) The human Jnk1 gene (GenBank Accession number: L26318) was amplified using PCR according to standard protocols with primers Jnk-top (SEQ ID NO:17) and Jnk-bottom/+stop (SEQ ID NO:19). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produced an EGFP-Jnk1 fusion (SEQ ID NO:44 &45) under the control of a CMV promoter.
- b) The human Jnk1 gene (GenBank Accession number: L26318) was amplified using PCR according to standard protocols with primers Jnk-top (SEQ ID NO:17) and Jnk-bottom/-stop (SEQ ID NO:18). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a Jnk1-EGFP fusion (SEQ ID NO:62 &63) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. HEK293, in which the EGFP-Jnk1 probe and/or the Jnk1-EGFP probe should change its cellular distribution from predominantly cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. anisomycin.

25

10

15

### Example 10:

Probes for detection of PKG redistribution.

Useful for monitoring signalling pathways involving changes in cyclic GMP levels, e.g. to identify compounds which modulate the activity of the pathway in living cells.

PGK, a cGMP-dependent serine/threonine protein kinase, mediates the guanylylcyclase/cGMP signal.

- a) The human PKG gene (GenBank Accession number: Y07512) is amplified using PCR according to standard protocols with primers PKG-top (SEQ ID NO:81) and PKG-bottom/+stop (SEQ ID NO:83). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-PKG fusion (SEQ ID NO:134 &135) under the control of a CMV promoter.
- b) The human PKG gene (GenBank Accession number: Y07512) is amplified using PCR according to standard protocols with primers PKG-top (SEQ ID NO:81) and PKG-bottom/-stop
   (SEQ ID NO: 82) . The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a PKG-EGFP fusion (SEQ ID NO:136 &137) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. A10, in which the EGFP-PKG probe and/or the PKG-EGFP probe should change its cellular distribution from cyto-plasmic to one associated with cytoskeletal elements within minutes in response to treatment with agents which raise nitric oxide (NO) levels.

# Example 11:

15

25

30

- 20 Probes for detection of IkappaB kinase redistribution.
  - Useful for monitoring signalling pathways leading to NFkappaB activation, e.g. to identify compounds which modulate the activity of the pathway in living cells.
  - IkappaB kinase, a serine/threonine kinase, is a component of a signalling pathway which is activated by a variety of inducers including cytokines, lymphokines, growth factors and stress.
  - a) The alpha subunit of the human IkappaB kinase gene (GenBank Accession number: AF009225) is amplified using PCR according to standard protocols with primers IKK-top (SEQ ID NO:96) and IKK-bottom/+stop (SEQ ID NO:98). The PCR product is digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-C1 (Clontech, Palo Alto;

GenBank Accession number U55763) digested with EcoR1and Acc65I. This produces an EGFP-IkappaB-kinase fusion (SEQ ID NO:120 &121) under the control of a CMV promoter.

b) The alpha subunit of the human IkappaB kinase gene (GenBank Accession number: AF009225) is amplified using PCR according to standard protocols with primers IKK-top (SEQ ID NO:96) and IKK-bottom/-stop (SEQ ID NO:97). The PCR product is digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and Acc65I. This produces an IkappaB-kinase-EGFP fusion (SEQ ID NO:122 &123) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the

EGFP-lkappaB-kinase probe and/or the lkappaB-kinase-EGFP probe should achieve a more
cytoplasmic distribution within seconds following stimulation with e.g. TNFalpha.

#### Example 12:

30

Probes for detection of CDK2 redistribution.

- Useful for monitoring signalling pathways of the cell cycle, e.g. to identify compounds which modulate the activity of the pathway in living cells.
  - CDK2, a cyclin-dependent serine/threonine kinase, is a component of the signalling system which regulates the cell cycle.
- a) The human CDK2 gene (GenBank Accession number: X61622) is amplified using PCR according to standard protocols with primers CDK2-top (SEQ ID NO:102) and CDK2-bottom/+stop (SEQ ID NO: 104). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-CDK2 fusion (SEQ ID NO:114 &115) under the control of a CMV promoter.
  - b) The human CDK2 gene (GenBank Accession number: X61622) is amplified using PCR according to standard protocols with primers CDK2-top (SEQ ID NO:102) and CDK2-bottom/-stop (SEQ ID NO:103). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a CDK2-EGFP fusion (SEQ ID NO:112 &113) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. HEK293 in which the EGFP-CDK2 probe and/or the CDK2-EGFP probe should change its cellular distribution from cytoplasmic in contact-inhibited cells, to nuclear location in response to activation with a number of growth factors, e.g. IGF.

5

# Example 13:

Probes for detection of Grk5 redistribution.

Useful for monitoring signalling pathways involving desensitization of G-protein coupled receptors, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Grk5, a G-protein coupled receptor kinase, is a component of signalling pathways involving membrane bound G-protein coupled receptors.

- a) The human Grk5 gene (GenBank Accession number: L15388) is amplified using PCR according to standard protocols with primers Grk5-top (SEQ ID NO:27) and Grk5-
- bottom/+stop (SEQ ID NO:29). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Grk5 fusion (SEQ ID NO:42 &43) under the control of a CMV promoter.
- b) The human Grk5 gene (GenBank Accession number: L15388) is amplified using PCR according to standard protocols with primers Grk5-top (SEQ ID NO:27) and Grk5-bottom/-stop (SEQ ID NO:28). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produces a Grk5-EGFP fusion (SEQ ID NO:60 &61) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. HEK293 expressing a rat dopamine D1A receptor, in which the EGFP-Grk5 probe and/or the Grk5-EGFP probe should change its cellular distribution from predominantly cytoplasmic to peripheral in response to activation of the signalling pathway with e.g. dopamine.

## 30 Example 14:

Probes for detection of Zap70 redistribution.

Useful for monitoring signalling pathways involving the T cell receptor, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Zap70, a tyrosine kinase, is a component of a signalling pathway which is active in e.g. T-cell differentiation.

- a) The human Zap70 gene (GenBank Accession number: L05148) is amplified using PCR according to standard protocols with primers Zap70-top (SEQ ID NO:105) and Zap70-bottom/+stop (SEQ ID NO:107). The PCR product is digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-C1 (GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Zap70 fusion (SEQ ID NO:108 &109) under the control of a CMV promoter.
- b) The human Zap70 gene (GenBank Accession number: L05148) is amplified using PCR according to standard protocols with primers Zap70-top (SEQ ID NO:105) and Zap70-bottom/-stop (SEQ ID NO:106). The PCR product is digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produces a Zap70-EGFP fusion (SEQ ID NO:110 &111) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-Zap70 probe and/or the Zap70-EGFP probe should change its cellular distribution from cytoplasmic to membrane-associated within seconds in response to activation of the T cell receptor signalling pathway with e.g. antibodies to CD3epsilon.

## Example 15:

25 Probes for detection of p85 redistribution.

Useful for monitoring signalling pathways involving PI-3 kinase, e.g. to identify compounds which modulate the activity of the pathway in living cells.

p85alpha is the regulatory subunit of PI3-kinase which is a component of many pathways involving membrane-bound tyrosine kinase receptors and G-protein-coupled receptors.

5

10

15

20

- a) The human p85alpha gene (GenBank Accession number: M61906) was amplified using PCR according to standard protocols with primers p85-top-C (SEQ ID NO:22) and p85-bottom/+stop (SEQ ID NO:23). The PCR product was digested with restriction enzymes Bgl2 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Bgl2 and BamH1. This produced an EGFP-p85alpha fusion (SEQ ID NO:48 &49) under the control of a CMV promoter.
- b) The human p85alpha gene (GenBank Accession number: M61906) was amplified using PCR according to standard protocols with primers p85-top-N (SEQ ID NO:20) and p85-bottom/-stop (SEQ ID NO:21). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produced a p85alpha-EGFP fusion (SEQ ID NO:66 &67) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. CHO expressing the human insulin receptor, in which the EGFP-p85 probe and/or the p85-EGFP probe may change its cellular distribution from cytoplasmic to membrane-associated within minutes in response to activation of the receptor with insulin.

#### Example 16:

10

15

Probes for detection of protein-tyrosine phosphatase redistribution.

- Useful for monitoring signalling pathways involving tyrosine kinases, e.g. to identify compounds which modulate the activity of the pathway in living cells.
  - Protein-tyrosine phosphatase1C, a tyrosine-specific phosphatase, is an inhibitory component in signalling pathways involving e.g. some growth factors.
- a) The human protein-tyrosine phosphatase 1C gene (GenBank Accession number: X62055) is amplified using PCR according to standard protocols with primers PTP-top (SEQ ID NO:99) and PTP-bottom/+stop (SEQ ID NO:101). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and EcoR1. This produces an EGFP-PTP fusion (SEQ ID NO:116 &117) under the control of a CMV promoter.

10

30

b) The human protein-tyrosine phosphatase 1C gene (GenBank Accession number: X62055) is amplified using PCR according to standard protocols with primers PTP-top (SEQ ID NO:99) and PTP-bottom/-stop (SEQ ID NO:100). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and EcoR1. This produces a PTP-EGFP fusion (SEQ ID NO:118 &119) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. MCF-7 in which the EGFP-PTP probe and/or the PTP-EGFP probe should change its cellular distribution from cytoplasm to the plasma menbrane within minutes in response to activation of the growth inhibitory signalling pathway with e.g. somatostatin.

# Example 17:

Probes for detection of Smad4 redistribution.

Useful for monitoring signalling pathways involving most members of the transforming growth factor-beta family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Smad4, a signal transducer, is a common component of signalling pathways induced by various members of the TGFbeta family of cytokines.

- a) The human Smad4 gene (GenBank Accession number: U44378) was amplified using PCR according to standard protocols with primers Smad4-top and Smad4-bottom/+stop (SEQ ID NO:35). The PCR product was digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produce an EGFP-Smad4 fusion (SEQ ID NO:52 &53) under the control of a CMV promoter.
  - b) The human Smad4 gene (GenBank Accession number: U44378) was amplified using PCR according to standard protocols with primers Smad4-top (SEQ ID NO:33) and Smad4-bottom/-stop (SEQ ID NO:34). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produced a Smad4-EGFP fusion (SEQ ID NO:76 &77) under the control of a CMV promoter.

WO 98/45704 PCT/DK98/00145

52

The resulting plasmids are transfected into a cell line, e.g. HEK293 in which the EGFP-Smad4 probe and/or the Smad4-EGFP probe should change its cellular distribution within minutes from cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. TGFbeta.

5

10

#### Example 18:

Probes for detection of Stat5 redistribution.

Useful for monitoring signalling pathways involving the activation of tyrosine kinases of the Jak family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Stat5, signal transducer and activator of transcription, is a component of signalling pathways which are induced by e.g. many cytokines and growth factors.

- a) The human Stat5 gene (GenBank Accession number: L41142) was amplified using PCR according to standard protocols with primers Stat5-top (SEQ ID NO:30) and Stat5-bottom/+stop (SEQ ID NO:32). The PCR product was digested with restriction enzymes Bgl2 and Acc651, and ligated into pEGFP-C1 (Clontech; Palo Alto; GenBank Accession number U55763) digested with Bgl2 and Acc651. This produced an EGFP-Stat5 fusion (SEQ ID NO:54 &55) under the control of a CMV promoter.
- b) The human Stat5 gene (GenBank Accession number: L41142) was amplified using PCR according to standard protocols with primers Stat5-top (SEQ ID NO:30) and Stat5-bottom/stop (SEQ ID NO:331). The PCR product was digested with restriction enzymes Bgl2 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Bgl2 and Acc65I. This produced a Stat5-EGFP fusion (SEQ ID NO:78
   &79) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. MIN6 in which the EGFP-Stat5 probe and/or the Stat5-EGFP probe should change its cellular distribution from cyto-plasmic to nuclear within minutes in response to activation signalling pathway with e.g. prolactin.

30

# Example 19:

Probes for detection of NFAT redistribution.

Useful for monitoring signalling pathways involving activation of NFAT, e.g. to identify compounds which modulate the activity of the pathway in living cells.

- 5 NFAT, an activator of transcription, is a component of signalling pathways which is involved in e.g. immune responses.
- a) The human NFAT1 gene (GenBank Accession number: U43342) is amplified using PCR according to standard protocols with primers NFAT-top (SEQ ID NO:84) and NFAT bottom/+stop (SEQ ID NO:86). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and EcoR1. This produces an EGFP-NFAT fusion (SEQ ID NO:130 &131) under the control of a CMV promoter.
- b) The human NFAT gene (GenBank Accession number: U43342) is amplified using PCR according to standard protocols with primers NFAT-top (SEQ ID NO:84) and NFAT-bottom/stop (SEQ ID NO:85). The PCR product is digested with restriction enzymes Xho1 and E-coR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and EcoR1. This produces an NFAT-EGFP fusion (SEQ ID NO:132 &133) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-NFAT probe and/or the NFAT-EGFP probe should change its cellular distribution from cytoplasmic to nuclear within minutes in response to activation of the signalling pathway with e.g. antibodies to CD3epsilon.

#### 25 Example 20:

Probes for detection of NFkappaB redistribution.

Useful for monitoring signalling pathways leading to activation of NFkappaB, e.g. to identify compounds which modulate the activity of the pathway in living cells.

NFkappaB, an activator of transcription, is a component of signalling pathways which are responsive to a varity of inducers including cytokines, lymphokines, some immunosuppressive agents.

- a) The human NFkappaB p65 subunit gene (GenBank Accession number: M62399) is amplified using PCR according to standard protocols with primers NFkappaB-top (SEQ ID NO:87) and NFkappaB-bottom/+stop (SEQ ID NO:89). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-NFkappaB fusion (SEQ ID NO:142 & 143) under the control of a CMV promoter.
  - b) The human NFkappaB p65 subunit gene (GenBank Accession number: M62399) is amplified using PCR according to standard protocols with primers NFkappaB-top (SEQ ID NO:87) and NFkappaB-bottom/-stop (SEQ ID NO:88). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces an NFkappaB-EGFP fusion (SEQ ID NO:140 & 141) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-NFkappaB probe and/or the NFkappaB-EGFP probe should change its cellular distribution from cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. TNFalpha.

#### Example 21:

15

20

25

30

Probe for detection of RhoA redistribution.

Useful for monitoring signalling pathways involving RhoA, e.g. to identify compounds which modulate the activity of the pathway in living cells.

RhoA, a small GTPase, is a component of many signalling pathways, e.g. LPA induced cytoskeletal rearrangements.

The human RhoA gene (GenBank Accession number: L25080) was amplified using PCR according to standard protocols with primers RhoA-top (SEQ ID NO:92) and RhoA-bottom/+stop (SEQ ID NO:93). The PCR product was digested with restriction enzymes

Hind3 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Hind3and BamH1. This produced an EGFP-RhoA fusion (SEQ ID NO:126 &127) under the control of a CMV promoter.

The resulting plasmid is transfected into a suitable cell line, e.g. Swiss3T3, in which the

EGFP-RhoA probe should change its cellular distribution from a reasonably homogenous to
a peripheral distribution within minutes of activation of the signalling pathway with e.g. LPA.

Example 22:

Probes for detection of PKB redistribution.

Useful for monitoring signalling pathways involving PKB e.g. to identify compounds which modulate the activity of the pathway in living cells.

PKB, a serine/threonine kinase, is a component in various signalling pathways, many of which are activated by growth factors.

- a) The human PKB gene (GenBank Accession number: M63167) is amplified using PCR according to standard protocols with primers PKB-top (SEQ ID NO:36) and PKB-bottom/+stop (SEQ ID NO:80). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-PKB fusion (SEQ ID NO:138 & 139) under the control of a CMV promoter.
- b) The human PKB gene (GenBank Accession number: M63167) was amplified using PCR according to standard protocols with primers PKB-top (SEQ ID NO:36) and PKB-bottom/stop (SEQ ID NO:37). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a PKB-EGFP fusion (SEQ ID NO:70 &71) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. CHO expressing the human insulin receptor, in which the EGFP-PKB probe and/or the PKB-EGFP probe cycles between cytoplasmic and membrane locations during the activation-deactivation process following addition of insulin. The transition should be apparent within minutes.

#### REFERENCES:

- Adams, S.R., Harootunian, A.T., Buechler, Y.J., Taylor, S.S. & Tsien, R.Y. (1991) Nature 349, 694-697
- Blobe, G.C., Stribling, D.S., Fabbro, D., Stabel, S & Hannun, Y.A. (1996) J. Biol. Chem. 271, 15823-15830
  - Chalfie, M., Tu, Y., Euskirchen, G., Ward, W.W. & Prasher, D.C. (1994) Science 263, 802-805
  - Cossette, L.J., Hoglinger, O., Mou, L.J. & Shen, S.H. (1997) Exp. Cell Res. 223, 459-466
- DeBernardi, M.A. & Brooker, G. (1996) Proc. Natl. Acad. Sci. USA 93, 4577-4582
   Farese, R.V.. (1992) Biochem. J. 288, 319-323
  - Fulop Jr., T., Leblanc, C., Lacombe, G. & Dupuis, G. (1995) FEBS Lett. 375, 69-74

    Godson, C., Masliah, E., Balboa, M.A., Ellisman, M.H. & Insel, P.A. (1996) Blochem. Biophys. Acta 1313, 63-71
- 15 Khalil, R.A., Lajoie, C., Resnick, M.S. & Morgan, K.G. (1992) American Physiol. Society c, 714-719
  - Sano, M., Kohno, M. & Iwanaga, M. (1995) Brain Res. **688**, 213-218

    Bastiaens, P.I.H. & Jovin, T.M. (1996) Proc. Natl. Acad. Sci. USA **93**, 8407-8412

    Schmidt, D.J., Ikebe, M., Kitamura, K., & Fay, F.S. (1997) FASEB J. **11**, 2924 (Abstract)
- Sakai, N., Sasaki, K., Hasegawa, C., Ohkura, M., Suminka, K., Shirai, Y. & Saito, N. (1996) Soc. Neuroscience 22, 69P (Abstract)
  - Sakai, N., Sakai, K. Hasegawa, C., Ohkura, M., Sumioka, ., Shirai, Y., & Naoaki, S. (1997) Japanese Journal of Pharmacology 73, 69P (Abstract of a meeting held 22-23 March)

WO 98/45704 PCT/DK98/00145

57

# SEQUENCE LISTING

5	(1) GENERAL INFORMATION
	(i) APPLICANT: NovoNordisk, BioImage
10	(ii) TITLE OF THE INVENTION: A Method of Detecting Cellular Translocation of Biologically Active Polypeptides Using Fluorescense Imaging
	(iii) NUMBER OF SEQUENCES: 143
15	<ul><li>(iv) CORRESPONDENCE ADDRESS:</li><li>(A) ADDRESSEE: NovoNordisk, BioImage</li><li>(B) STREET: Mørkhøjbygade 28</li><li>(C) CITY: Søborg</li></ul>
20	(D) STATE: DK (E) COUNTRY: DENMARK
	(F) ZIP: 2860
25	(v) COMPUTER READABLE FORM:  (A) MEDIUM TYPE: Diskette  (B) COMPUTER: IBM Compatible  (C) OPERATING SYSTEM: DOS
	(D) SOFTWARE: FastSEQ for Windows Version 2.0
30	<pre>(viii) ATTORNEY/AGENT INFORMATION:   (A) NAME: , PV&amp;P R   (B) REGISTRATION NUMBER:   (C) REFERENCE/DOCKET NUMBER:</pre>
35	
	(2) INFORMATION FOR SEQ ID NO:1:
40	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 53 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:
	TTGGACACAA GCTTTGGACA CGGCGCGCCA TGAGTAAAGG AGAAGAACTT TTC 53
<b>E</b> 0	(2) INFORMATION FOR SEQ ID NO:2:
50	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 53 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>
55	(D) TOPOLOGY: linear

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:	
_	GTCATCTTCT CGAGTCTTAC TCCTGAGGTT TGTATAGTTC ATCCATGCCA TGT	53
5	(2) INFORMATION FOR SEQ ID NO:3:	
10	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 54 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
15	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:	
	TTGGACACAA GCTTTGGACA CCCTCAGGAT ATGGGCAACG CCGCCGCCGC CAAG	54
20	(2) INFORMATION FOR SEQ ID NO:4:	
20	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 55 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
25	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
23	(b) Torollog1. Tilled1	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:	
30	GTCATCTTCT CGAGTCTTTC AGGCGCGCCC AAACTCAGTA AACTCCTTGC CACAC	55
	(2) INFORMATION FOR SEQ ID NO:5:	
35	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 55 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:	
	TTGGACACAA GCTTTGGACA CCCTCAGGAT ATGGCTGACG TTTACCCGGC CAACG	55
45	(2) INFORMATION FOR SEQ ID NO:6:	
50	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 55 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
55	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:	
55	GTCATCTTCT CGAGTCTTTC AGGCGCGCCC TACTGCACTT TGCAAGATTG GGTGC	55 58

WO 98/45704 PCT/DK98/00145

59

	(2) INFORMATION FOR SEQ ID NO:7:	
5	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 64 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:	
a ei	TTGGACACAA GCTTTGGACA CCCTCAGGAT ATGGCGGCGG CGGCGGCGGC TCCGGGGGGC	60 64
15	(2) INFORMATION FOR SEQ ID NO:8:	
20	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 55 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
25	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:	
•	GTCATCTTCT CGAGTCTTTC AGGCGCCCCC GGGGCCCCTCT GGCGCCCCTG GCTGG	55
30	(2) INFORMATION FOR SEQ ID NO:9:  (i) SEQUENCE CHARACTERISTICS:	
35	<ul><li>(A) LENGTH: 30 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:	
40	TAGAATTCAA CCATGGCGGC GGCGGCGGCG	30
	(2) INFORMATION FOR SEQ ID NO:10:	
45	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 29 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
50	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:	
	TAGGATCCCT AGGGGGCCTC CAGCACTCC	29
55	(2) INFORMATION FOR SEQ ID NO:11:	

5	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 31 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:	
10	TACTCGAGTA ACCATGGCGG CGGCGGCGGC G	31
	(2) INFORMATION FOR SEQ ID NO:12:	
15	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 25 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:	
	TAGGATCCAT AGATCTGTAT CCTGG	25
25	(2) INFORMATION FOR SEQ ID NO:13:	·
30	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 26 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
35	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:	. 26
-	TAGGATCCTT AAGATCTGTA TCCTGG  (2) INFORMATION FOR SEQ ID NO:14:	20
40	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 28 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single	
45	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:	
ro	ATCTCGAGGG AAAATGTCTC AGGAGAGG	28
50	(2) INFORMATION FOR SEQ ID NO:15:	
55	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 28 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>	

61 .

	(D) TOPOLOGY: linear	
_	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:	
5	ATGGATCCTC GGACTCCATC TCTTCTTG	28
	(2) INFORMATION FOR SEQ ID NO:16:	
10	(i) SEQUENCE CHARACTERISTICS:	
, •	(A) LENGTH: 29 base pairs (B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
15	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:	
20	ATGGATCCTC AGGACTCCAT CTCTTCTTG	29
20	(2) INFORMATION FOR SEQ ID NO:17:	
	(i) SEQUENCE CHARACTERISTICS:	
25	(A) LENGTH: 28 base pairs (B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:	
	GTCTCGAGCC ATCATGAGCA GAAGCAAG	28
35	(2) INFORMATION FOR SEQ ID NO:18:	
00	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 27 base pairs	
	(B) TYPE: nucleic acid (C) STRANDEDNESS: single	
40	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:	
45		27
45	GTGGATCCCA CTGCTGCACC TGTGCTA	21
	(2) INFORMATION FOR SEQ ID NO:19:	
50	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs	
ψŪ	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
55		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:	

	GTGGATCCTC ACTGCTGCAC CTGTGCTA	28
_	(2) INFORMATION FOR SEQ ID NO:20:	
5	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 40 base pairs	
	(B) TYPE: nucleic acid (C) STRANDEDNESS: single	
10	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:	
15	CGCGAATTCC GCCACCATGA GTGCTGAGGG GTACCAGTAC	40
	(2) INFORMATION FOR SEQ ID NO:21:	
	(i) SEQUENCE CHARACTERISTICS:	
20	(A) LENGTH: 32 base pairs (B) TYPE: nucleic acid	
	(B) TYPE: nucleic acid (C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
25		
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:	
	CGCGGATCCT GTCGCCTCTG CTGTGCATAT AC	32
30	(2) INFORMATION FOR SEQ ID NO:22:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 30 base pairs	
35	(B) TYPE: nucleic acid (C) STRANDEDNESS: single	
33	(D) TOPOLOGY: linear	
	(vi) ORIGINAL SOURCE:	
	(A) ORGANISM: p85-top-C	
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:	
	GGGAGATCTA TGAGTGCTGA GGGGTACCAG	30
45	(2) INFORMATION FOR SEQ ID NO:23:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 34 base pairs	
50	<ul><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>	
30	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:	
55	GGGCGGATCC TCATCGCCTC TGCTGTGCAT ATAC	34
		62

	(2) INFORMATION FOR SEQ ID NO:24:	
5	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 33 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:	·
	GTGAATTCGA CCATGTCGTC CATCTTGCCA TTC	33
15	(2) INFORMATION FOR SEQ ID NO:25:	
20	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 31 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
25	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:	31
	GTGGTACCCA TGACATGCTT GAGCAACGCA C	31
30 35	(2) INFORMATION FOR SEQ ID NO:26:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 32 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:	
40	GTGGTACCTT ATGACATGCT TGAGCAACGC AC (2) INFORMATION FOR SEQ ID NO:27:	32
45	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 31 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
50	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:	
	GTGAATTCGT CAATGGAGCT GGAAAACATC G	31
55	(2) INFORMATION FOR SEQ ID NO:28:	
00	(i) SEQUENCE CHARACTERISTICS:	

	- 04	
5	<ul><li>(A) LENGTH: 30 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:	
10	GTGGATCCCT GCTGCTTCCG GTGGAGTTCG	30
	(2) INFORMATION FOR SEQ ID NO:29:	
15	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 31 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:	
	GTGGATCCCT AGCTGCTTCC GGTGGAGTTC G	31
25	(2) INFORMATION FOR SEQ ID NO:30:	
- <b>-</b>	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 32 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
30	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(x1) SEQUENCE DESCRIPTION: SEQ ID NO:30:	
35	GTAGATCTAC CATGGCGGGC TGGATCCAGG CC	32
	(2) INFORMATION FOR SEQ ID NO:31:	
40	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 31 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
45	(with Grovery Description, one of the second	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:	
	GTGGTACCCA TGAGAGGGAG CCTCTGGCAG A	31
50	(2) INFORMATION FOR SEQ ID NO:32:	
	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 31 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
55	(C) STRANDEDNESS: single	

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:	
5	GTGGTACCTC ATGAGAGGGA GCCTCTGGCA G	31
	(2) INFORMATION FOR SEQ ID NO:33:	
10	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 33 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
15		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:	
	GTGAATTCAA CCATGGACAA TATGTCTATT ACG	33
20	(2) INFORMATION FOR SEQ ID NO:34:	
	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 31 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
25	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:	
	GTGGATCCCA GTCTAAAGGT TGTGGGTCTG C	31
	(2) INFORMATION FOR SEQ ID NO:35:	
35	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 32 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>	
40	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:	
45	GTGGATCCTC AGTCTAAAGG TTGTGGGTCT GC	32
70	(2) INFORMATION FOR SEQ ID NO:36:	
50	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 27 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
55 ·	(xi) SEOUENCE DESCRIPTION: SEO ID NO:36:	

	66	
	GTCTCGAGGC ACCATGAGCG ACGTGGC	27
	(2) INFORMATION FOR SEQ ID NO:37:	
5	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single	
10	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:	
15	TGGGATCCGA GGCCGTGCTG CTGGCCG	27
13	(2) INFORMATION FOR SEQ ID NO:38:	
20	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 1896 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
25	(ii) MOLECULE TYPE: cDNA (ix) FEATURE:	
30	<ul><li>(A) NAME/KEY: Coding Sequence</li><li>(B) LOCATION: 11891</li><li>(D) OTHER INFORMATION:</li><li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:</li></ul>	
35	ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15	48
	GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30	96
40		• 4.4
	GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 35 40 45	144
45	TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 50 55 60	192
50	CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 65 70 75 80	240
55	CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 90 95	288

							6/					
			TTC Phe 100								3	136
5			GAG Glu								3	884
10	 		AAG Lys								4	132
15			AGC Ser								4	80
			GTG Val								5	528
20	 		GCC Ala 180									576
25			CTG Leu								€	524
30			CCC Pro									572
35	 		GCC Ala								•	720
40	 		TCT Ser								•	768
40			GGG Gly 260								1	816
45			GTC Val			Glu				_	;	864
50		Gly								GCG Ala		912
55	Gly				Ala			Arg		GTG Val 320		960

										68							
·			.c "Liy	. Б	325	5	. Pr	o Ph	e Glı	1 His 330	Glı O	n Thi	Ty	Cy:	33!		1008
5			u Ai	34	0	e GID	1 116	e re	1 Let 345	Arg	<b>y</b> Ph∈	≥ Arg	His	350	ı Ası	GTC 1 Val	1056
10	,110		35	5 5	y Asp	, TTG	. rea	360	j Ala )	Ser	Thr	: Leu	Glu 365	Ala	Met	AGA Arg	1104
15	GA7 Asp	7 GT 7 Va: 37	r ry.	C ATT	r GTG e Val	CAG Gln	GAC Asp 375	) Leu	ATG Met	GAG Glu	ACT	GAC Asp 380	CTG Leu	TAC Tyr	AAC Lys	TTG Leu	1152
20	385	. TÀF	s ser	GIR	CAG Gln	190	Ser	Asn	qeA	His	11e 395	Сув	Tyr	Phe	Leu	Tyr 400	1200
	GIII	TIE	: ьет	. Arg	GGC Gly 405	Leu	ГÀ2	Tyr	Ile	His 410	Ser	Ala	Asn	Val	Leu 415	His	1248
25	CGA Arg	GAT Asp	CTA Leu	AAG Lys 420	Pro	TCC Ser	AAC Asn	CTG Leu	CTC Leu 425	AGC Ser	AAC Asn	ACC Thr	ACC Thr	TGC Cys 430	GAC Asp	CTT Leu	1296
30	AAG Lys	ATT	TGT Cys 435	Asp	TTC Phe	GGC Gly	CTG Leu	GCC Ala 440	CGG Arg	ATT Ile	GCC Ala	GAT Asp	CCT Pro 445	GAG Glu	CAT His	GAC Asp	1344
35	CAC His	ACC Thr 450	GGC	TTC Phe	CTG Leu	ACG Thr	GAG Glu 455	TAT Tyr	GTG Val	GCT Ala	ACG Thr	CGC Arg 460	TGG Trp	TAC Tyr	CGG Arg	GCC Ala	1392
40	465	GIU	116	wec		470	ser	Lys	Gly	Tyr	Thr 475	Lys	Ser	Ile	Asp	Ile 480	1440
	TGG	TCT Ser	GTG Val	GGC Gly	TGC Cys 485	ATT Ile	CTG Leu	GCT Ala	Glu	ATG Met 490	CTC Leu	TCT . Ser .	AAC Asn .	Arg	CCC Pro 495	ATC Ile	1488
45	TTC Phe	CCT Pro	GGC Gly	AAG Lys 500	CAC His	TAC (	CTG Leu	qaA	CAG Gln 505	CTC . Leu .	AAC Asn	CAC :	Ile :	CTG Leu 510	GGC Gly	ATC Ile	1536
50	CTG Leu	GGC Gly	TCC Ser 515	CCA Pro	TCC (	CAG ( Gln (	stu .	GAC Asp 520	CTG .	AAT ' Asn (	TGT :	Ile :	ATC I Ile I 525	AAC .	ATG Met	AAG Lys	1584
55	ALU.	CGA Arg 530	AAC Asn	TAC Tyr	CTA ( Leu (	in s	CT Ser :	CTG Leu	CCC ! Pro :	rcc : Ser 1	Lys :	ACC I Thr I	AAG (	TG (	GCT Ala	TGG Trp	1632

		AAG Lys															1680
5		ATG Met															1728
10		GCT Ala															1776
15		GCC Ala										Leu					1824
20		GAG Glu 610															1872
20		GGA Gly					-	CTAG									1896
25																	
30		t)	(A) (B) (C)	LENG TYPI STR	FTH: E: ar ANDEI	CHARA 631 mino ONESS Y: li	amin acio 3: si	no ao i ingle	cids								
35	4	(7	7) FI	RAGMI	ENT :	TYPI	int	terna	al								
		()	(1) }	EEQUI	SNCE	DES	CRIP.	LION	: SE	O ID	NO:3	39:					
40	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	
		Glu	Leu	Asp 20	_	Asp	Val	Asn	Gly 25		Lys	Phe	Ser	Val 30		Gly	
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile	
45	Сув	Thr 50		Gly	Lys	Leu	Pro 55		Pro	Trp	Pro	Thr 60		Val	Thr	Thr	
	Leu 65	Thr	Tyr	Gly	Val	Gln 70	CAR	Phe	Ser	Arg	_	Pro	Asp	His	Met	Lys 80	
50		His	Asp	Phe	Phe 85		Ser	Ala	Met	Pro 90	75 Glu	Gly	Tyr	Val	Gln 95		
J-	Arg	Thr	Ile			Lys	Asp	Asp	_		Tyr	Lys	Thr			Glu	
	Val	Lys	Phe	100 Glu	Gly	Asp	Thr	Leu 120	105 Val	Asn	Arg	Ile	Glu 125	110 Leu	Lys	Gly	
55	Ile	Asp 130	Phe	ГĀЗ	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140		Leu	Glu	Tyr	

	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	qaA	Lys	Gln	ГÀЗ	Asn 160
	Gly	Ile	Lys	Val	Asn 165	Phe	rys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser
5	•			180	_		-		185					Gly 190	_	_
			195			_		200	-				205	Ser		
10		210					215					220		Leu		
	Val 225	Thr	Ala	Ala	Gly	11e 230	Thr	Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	Lys	Ser 240
	-		_		245					250				Ala	255	
15				260	_	_	_	-	265			_		Glu 270		
	_		275					280					285	Gln		
20		290	-		_	-	295					300		Glu		
	305	_				310		_	_		315		_	Thr		320
			_		325					330			- ·	Сув	335	
25			-	340					345	_		_		Glu 350		
			355					360					365	Ala		
30	-	370	_				375					380		Tyr		
	385	_				390			_		395			Phe		400
05				_	405		_	_		410				Val	415	
35	_	_		420					425					Cys 430		
	-		435	_		-		440	_			_	445	Glu		
40		450	_				455	_				460	_	Tyr		
	465					470		-	-	_	475			Ile		480
1E	_				485					490	,			Arg	495	
45			-	500		_		_	505					Leu 510	_	
		-	515					520			-		525	Asn		
50		530					535					540		Val		
	545	_				550		_		_	555			Leu		560
<i></i>					565					570	)			Glu	575	
55	ьeu	ATA	. n18	9ro 580		nen	GIU	GIU	Tyr 585		Asp	rro	inr	Asp 590		PIC

	Val Ala	Glu G:	lu Pro	Phe Thr	Phe	Ala	Met	Glu	Leu	Asp 605	Asp	Leu	Pro	
	Lys Glu 610		eu Lys	Glu Leu 615	Ile	Phe	Gln		Thr 620		Arg	Phe	Gln	
5	Pro Gly 625	Val Le	eu Glu	Ala Pro 630	*									
		(2)	INFORMA	TION FO	R SEQ	ID	NO : 4	0:						
10	(:	(A) LI (B) T (C) S	ENGTH: YPE: nu TRANDED	HARACTE 1818 ba cleic a NESS: s : linea	se pa cid ingle	irs								
15		ii) MOI ix) FE		TYPE: c	DNA									
20		(B)	LOCATIO	Y: Codi N: 1 NFORMAT	1815	quen	ce							
	(:	xi) SE	QUENCE	DESCRIP	TION:	SEQ	ID	NO:4	:0:					
25	ATG GTG Met Val 1													48
30	GTC GAG Val Glu	Leu A												96
35	GAG GGC Glu Gly													144
40	TGC ACC Cys Thr 50													192
40	CTG ACC Leu Thr 65													240
45	CAG CAC													288
50	CGC ACC	lle P		AAG GAG Lys Asp										336
55				GAC ACC										384

								12					
							AAC Asn						432
5							TAT Tyr						480
10							ATC Ile						528
15	GTG Val						CAG Gln						576
							CAC His				_		624
20							CGC Arg				_	_	672
25							CTC Leu					TCC Ser 240	720
30							ATG Met				_		768
35		-					TTC Phe						816
							GCC Ala 280						864
40			Leu				GTT Val			Ile			912
45		His				Gln					_	CTA Leu 320	960
50					Glu				Ile			CGG	1008
55				Glu				Val			Asp	Leu	1056

										13							
		GAG Glu															1104
5		CAT His 370															1152
10		CAT His															1200
15		CTG Leu															1248
		GTT Val															1296
20		GCC Ala															1344
25		TAT Tyr 450															1392
30		ATG Met															1440
35		CTG Leu															1488
		AAT Asn															1536
40	CCG Pro	CAC His	AAA Lys 515	Asn	AAG Lys	GTG Val	CCG Pro	TGG Trp 520	Asn	AGG Arg	TTG Leu	TTC Phe	CCA Pro 525	AAC Asn	GCT Ala	GAC Asp	1584
45		AAA Lys 530	Ala					Asp					Phe			CAC His	1632
50	AAG Lys 545	Arg	ATT	GAA Glu	GTI Val	GAA Glu 550	Glm	GCI Ala	CTG Leu	GCC	CAC His	Pro	TAC Tyr	CTG Leu	GAG Glu	CAG Gln 560	1680
55						Asp					Glu					TTT Phe	1728

										74							
														GAA Glu 590			1776
5					GCT Ala									TAA			1818
10			(2)	INF	ORMA	\TION	i Foi	R SE(	QI Q	NO:4	1:						
15		i)	(A) (B) (C)	LENG TYPE STRA	ICE ( STH: S: an ANDEI OLOGY	605 nino NESS	amin acio 3: s:	no ad i ingle	cids								
20		(1	li) M /) FF	OLEC RAGME	CULE	TYPI YPE :	E: p:	rote: terna	al								
		()	(i) S	EQUE	ENCE	DESC	CRIP	rion	: SE(	O ID	NO:	11:					
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	
25		Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val	Ser	Gly	•
	Glu	Gly	Glu 35	Gly	qaA	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	ГÀВ	Phe	Ile	
30	Сув	Thr 50		Gly	Lys	Leu	Pro 55		Pro	Trp	Pro	Thr	Leu	Val	Thr	Thr	
	Leu 65		Tyr	Gly	Val	Gln 70		Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80	
		His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Cly	Tyr	Val	Gln 95	Glu	
35	Arg	Thr	Ile	Phe 100	Phe	ГХа	Aap	Asp	Gly 105	Asn	Tyr	ГÀв	Thr	Arg 110	Ala	Glu	
	Val	Lys	Phe 115	Glu	Gly	qaA	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	ГÀв	Gly	
40	Ile	Asp		-	Glu	_	_			Leu	_	His 140		Leu	Glu	Tyr	
	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155		Lув	Gln	Lys	Asn 160	
	Gly	Ile	Lys	Val	Asn 165	Phe	ГЛа	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser	
45	Val	Gln	Leu	Ala 180	qaA	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly	
	Pro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200		Leu	Ser	Thr	Gln 205		Ala	Leu	
50	Ser	Lys 210	qaA	Pro	Asn	Glu	Lys 215	Arg		His	Met	Val 220		Leu	Glu	Phe	
	Val 225		Ala	Ala	Gly	Ile 230		Leu	Gly	Met	Asp 235		Leu	Tyr	Lys	Ser 240	
			Arg	Ser	Arg 245	Val		Met	Ala	Ala 250	Ala		Ala	Ala	Gly 255	Pro	
55	Glu	Met	Val	Arg 260	_	Gln	Val	Phe	Asp 265		Gly	Pro	Arg	Tyr 270		Asn	

PCT/DK98/00145 WO 98/45704

75

```
Leu Ser Tyr Ile Gly Glu Gly Ala Tyr Gly Met Val Cys Ser Ala Tyr
                                  280
     Asp Asn Leu Asn Lys Val Arg Val Ala Ile Lys Lys Ile Ser Pro Phe
                              295
                                                  300
5
     Glu His Gln Thr Tyr Cys Gln Arg Thr Leu Arg Glu Ile Lys Ile Leu
                          310
                                              315
     Leu Arg Phe Arg His Glu Asn Ile Ile Gly Ile Asn Asp Ile Ile Arg
                                          330
     Ala Pro Thr Ile Glu Gln Met Lys Asp Val Tyr Ile Val Gln Asp Leu
10
                                      345
     Met Glu Thr Asp Leu Tyr Lys Leu Leu Lys Thr Gln His Leu Ser Asn
                                  360
     Asp His Ile Cys Tyr Phe Leu Tyr Gln Ile Leu Arg Gly Leu Lys Tyr
                             375
                                                 380
15
     Ile His Ser Ala Asn Val Leu His Arg Asp Leu Lys Pro Ser Asn Leu
                         390
                                             3<del>9</del>5
     Leu Leu Asn Thr Thr Cys Asp Leu Lys Ile Cys Asp Phe Gly Leu Ala
                      405
                                          410
     Arg Val Ala Asp Pro Asp His Asp His Thr Gly Phe Leu Thr Glu Tyr
20
                  420
                                     425
     Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Ser Lys
                                 440
     Gly Tyr Thr Lys Ser Ile Asp Ile Trp Ser Val Gly Cys Ile Leu Ala
                             455
                                                  460
25
     Glu Met Leu Ser Asn Arg Pro Ile Phe Pro Gly Lys His Tyr Leu Asp
                        470
                                             475
     Gln Leu Asn His Ile Leu Gly Ile Leu Gly Ser Pro Ser Gln Glu Asp
                                          490
                      485
     Leu Asn Cys Ile Ile Asn Leu Lys Ala Arg Asn Tyr Leu Leu Ser Leu
30
                                     505
      Pro His Lys Asn Lys Val Pro Trp Asn Arg Leu Phe Pro Asn Ala Asp
                                  520
      Ser Lys Ala Leu Asp Leu Leu Asp Lys Met Leu Thr Phe Asn Pro His
35
     Lys Arg Ile Glu Val Glu Gln Ala Leu Ala His Pro Tyr Leu Glu Gln
                          550
      Tyr Tyr Asp Pro Ser Asp Glu Pro Ile Ala Glu Ala Pro Phe Lys Phe
                                          570
      Asp Met Glu Leu Asp Asp Leu Pro Lys Glu Lys Leu Lys Glu Leu Ile
40
                                      585
      Phe Glu Glu Thr Ala Arg Phe Gln Pro Gly Tyr Arg Ser
               (2) INFORMATION FOR SEQ ID NO:42:
45
            (i) SEQUENCE CHARACTERISTICS:
             (A) LENGTH: 2529 base pairs
              (B) TYPE: nucleic acid
              (C) STRANDEDNESS: single
50
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: cDNA
```

(ix) FEATURE:

55

(A) NAME/KEY: Coding Sequence (B) LOCATION: 1...2526

76

## (D) OTHER INFORMATION:

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

		, -					 							
5	GTG Val													48
10	 GAG Glu													96
15	 GGC													144
20	ACC Thr 50													192
20	ACC Thr							Arg						240
25	 CAC His													288
30	ACC Thr													336
35	AAG Lys													384
40	GAC Asp 130													432
40	-					Val							AAC Asn 160	480
45	ATC Ile				Phe				Asn					528
50	CAG Gln			Asp				Asn				Asp	GGC Gly	576
55			Leu				Tyr				Ser		CTG Leu	624

							"						
	AAA Lys 210												672
5	 ACC Thr	 											720
10	 CTC Leu							Ser					768
15	ATC Ile												816
20	 AAG Lys												864
20	CAC His 290												912
25	TGC Cys												960
30	TTT Phe												1008
35	TCC Ser												1056
40	GGG Gly												1104
40	ATA Ile 370					Asp				Thr			1152
45	CTA Leu				Lys				Ala				1200
50				Arg				His				AGC Ser	1248
55	 	 -	Arg		_		Lys				Gln	CCG Pro	1296

78 .

										78 .							
4				AAC Asn													1344
5				GTC Val													1392
10				CGC Arg													1440
15				CTC Leu													1488
				AAC Asn 500													1536
20				ACC Thr													1584
25				AAC Asn												GCG Ala	1632
30				CTC Leu													1680
35				CTG Leu													1728
40				TCA Ser 580		-											1776
40	CTG Leu	ATC Ile	CGC Arg 595	GGC Gly	CGG Arg	GTG Val	GGC Gly	ACT Thr 600	GTT Val	GGC Gly	TAC Tyr	ATG Met	GCC Ala 605	CCC	GAA Glu	GTC Val	1824
45			Asn	CAG Gln												_	1872
50		Leu					Ile					Pro				CGT Arg 640	1920
55						Arg					Arg					ACG Thr	1968

								•	79		-	-	•	
		GAG Glu				_								2016
5		ATG Met												2064
10	_	GGG Gly 690	_	_	_	_								2112
15		AAG Lys												2160
20		CGC Arg												2208
		GTG Val												2256
25		TTC Phe												2304
30		ACA Thr 770												2352
35		CCG Pro												2400
40		CTG Leu												2448
		TCG Ser							Asn					2496
45		GTC Val								TAG				<b>2529</b>
50		,	·	) IN				~	NO:	43:				

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 842 amino acids
  - (B) TYPE: amino acid
- (C) STRANDEDNESS: single (D) TOPOLOGY: linear 55

80

## (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal

5		(x	:i) S	EQUE	NCE	DESC	RIPT	: NOI	SEC	ID.	NO:4	3:		•		
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
10	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
•		-	35	_	_			40					45	Lys		
	-	50					55					60		Val		
15	65		_			70					75			His		80
					85					90				Val Arg	95	
20	_			100					105					110 Leu		
		•	115					120					125	Leu		
25		130		_			135					140		Gln		
	145	_				150					155			Asp		160
	Val	Gln	Leu	Ala	165 Asp	His	Tyr	Gln	Gln	170 Asn		Pro	Ile	Gly	175 Asp	Gly
30	Pro	Val		180 Leu	Pro	Asp	Asn		185 Tyr	Leu	Ser	Thr		190 Ser	Ala	Leu
	Ser		195 Asp	Pro	Asn	Glu	Lys 215		Asp	His	Met	Val 220	205 Leu	Leu	Glu	Phe
35	Val 225	210 Thr	Ala	Ala	Gly	Ile 230			Gly	Met	Asp 235		Leu	Tyr	Lys	Ser 240
		Leu	Arg	Ser	Arg 245		Gln	Ala	Ser	Asn 250	Ser	Ser	Met	Glu	Leu 255	Glu
40				260					265					Gly 270		
	_	-	275					280					285			
	_	290					295					300		Asp		
45	305					310					315			Leu		320 Leu
					325					330	)				335	Glu
50				340	)				345	;				350 Ser		
			355	i				360	+				365	5		Lys
55		370	)				375	5				380	)			Ser
	385			-		390					395					400

	Val	His	Glu	Tyr	Leu 405	Arg	Gly	Glu	Pro	Phe 410	His	Glu	Tyr	Leu	Asp 415	Sea
	Met	Phe	Phe	Asp 420	Arg	Phe	Leu	Gln	Trp 425		Trp	Leu	Glu	Arg 430		Pro
5	Val	Thr	Lys 435	Asn	Thr	Phe	Arg	Gln 440	Tyr	Arg	Val	Leu	Gly 445	Lys	Gly	Gly
	Phe	Gly 450	Glu	Val	Cys	Ala	Cys 455	Gln	۷al	Arg	Ala	Thr 460	Gly	Lys	Met	Туз
10	Ala 465	Сув	Lys	Arg	Leu	Glu 470	Lys	Lys	Arg	Ile	Lys 475	Lys	Arg	Lys	Gly	Gl:
		Met	Ala	Leu	Asn 485		Lys	Gln	Ile	Leu 490		Lys	Val	Asn	Ser 495	
	Phe	Val	Val	Asn 500	Leu	Ala	Tyr	Ala	Tyr 505	Glu	Thr	Lys	qaA	Ala 510	Leu	Су
15	Leu	Val	Leu 515	Thr	Ile	Met	Asn	Gly 520	Gly	Asp	Leu	Lys	Phe 525		Ile	Туз
	Asn	Met 530	Gly	Asn	Pro	Gly	Phe 535	Glu	Glu	Glu	Arg	Ala 540	Leu	Phe	Tyr	Ala
20	Ala 545	Glu	Ile	Leu	Сув	Gly 550	Leu	Glu	Asp	Leu	His 555	Arg	Glu	Asn	Thr	Va. 560
	Tyr	Arg	Asp	Leu	Lys 565	Pro	Glu	Asn	Ile	Leu 570	Leu	Asp	Asp	Tyr	Gly 575	His
	Ile	Arg	Ile	Ser 580	qaA	Leu	Gly	Leu	Ala 585	Val	Lys	Ile	Pro	Glu 590	Gly	Asj
25	Leu	Ile	Arg 595	Gly	Arg	Val	Gly	Thr 600	Val	Gly	Tyr	Met	Ala 605	Pro	Glu	Va.
		610	naA				615					620				
30	625		Ile	_		630			_		635					640
	_		Lys		645					650		-			655	
			Val	660			_		665				-	670		_
35	_		Leu 675			_	_	680	_		_		685	_		
		690	Ala				695	_				700	-			
40	705		Arg			710					715					720
			Ala		725					730	_				735	
			Lys	740					745					750		
45	_		Ser 755		_			760			_		765			
	Glu	Thr 770	Glu	Cys	Phe	ГÀв	Glu 775	Leu	Asn	Val	Phe	Gly 780	Pro	Asn	Gly	Th:
50	Leu 785		Pro	qaA	Leu	Asn 790	Arg	Asn	His	Pro	Pro 795	Glu	Pro	Pro	Lys	80 Ey
	_		Leu		805			_	_	810					<b>B15</b>	
	Ser	Ser	Pro	Ser 820	Ser	Lys	Thr	Ser	Phe 825	Asn	His	His	Ile	Asn 830		As
55	His	Val	Ser 835		Asn	Ser	Thr	Gly 840		Ser						

		(2)	INI	FORM	ATION	I FOI	R SEC	Q ID	NO:4	14:				
5	 t)	(A) (B) (C)	LENG TYPE STR	VCE ( FTH: E: nu ANDEI OLOGY	1902 clei NESS	basic ac	se pa cid ingle	airs		•				
10	-	li) N ix) F		CULE JRE :	тург	E: cI	AAC							
15	(5	(B)	LOC	ME/KE CATIO HER I	ON: I	L1 RMATI	L899 CON:			NO.	14.			
				ENCE								 	 	
20				GGC Gly 5								 	 	48
<b>2</b> 5				GGC Gly										96
30				GAT Asp										144
				AAG Lys										192
35				GTG Val			_							240
40				TTC Phe 85										288
45				TTC Phe										336
50				GGC Gly										384
				GAG Glu										432
55				CAC His										480

								83						
	145				150				155				160	
5		 								ATC Ile				528
10										CCC Pro				576
		 -								ACC Thr		_		624
15										GTC Val 220				672
20										GAG Glu				720
25										AGA Arg				768
30										ACA Thr		_	CTG Leu	816
30										GGA Gly				864
35										AAT Asn 300				912
40										GCC Ala				960
45										Lys Lys				1008
<b>50</b>				Phe				Ser		GAA Glu			GAT Asp	1056
50			Val				Asp				Gln		ATT	1104
55													ATG Met	1152

	370				375					380				
5							TCT Ser							1200
10							AAA Lys							1248
							GCA Ala 425						_	1296
15							AGA Arg							1344
20							TTA Leu							1392
25							CTC Leu						_	1440
30							CAG Gln		Gly					1488
30							GTA Val 505							1536
35							GAG Glu							1584
40		Ala				Asn	AAA Lys							1632
45							ATA Ile			Ser				1680
50				Gln			TAC		Asn					1728
50			Ala					Ile				Lev	GAT Asp	1776
55													GAA Glu	1824

85 595 600 605 GTT ATG GAC TTG GAG GAG AGA ACC AAG AAT GGA GTT ATA CGG GGG CAG 1872 Val Met Asp Leu Glu Glu Arg Thr Lys Asn Gly Val Ile Arg Gly Gln 5 615 620 CCC TCT CCT TTA GCA CAG GTG CAG CAG TGA 1902 Pro Ser Pro Leu Ala Gln Val Gln Gln 630 10 (2) INFORMATION FOR SEQ ID NO:45: (i) SEQUENCE CHARACTERISTICS: 15 (A) LENGTH: 633 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 20 (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45: 25 Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 10 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 30 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 55 60 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 75 35 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 40 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 135 140 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 45 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 165 170 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 50 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 55 Gly Leu Arg Ser Arg Ala Arg Ala Ile Met Ser Arg Ser Lys Arg Asp

PCT/DK98/00145 WO 98/45704

	Asn	Asn	Phe	Tyr 260	Ser	Val	Glu	Ile	Gly 265	Asp	Ser	Thr	Phe	Thr 270	Val	Leu
	ГÀа	Arg	Tyr 275	Gln	Asn	Leu	Lys	Pro 280	Ile	Gly	Ser	Gly	Ala 285	Gln	Gly	Ile
5	Val	Cys 290	Ala	Ala	Tyr	Asp	Ala 295	Ile	Leu	Glu	Arg	Asn 300	Val	Ala	Ile	Lys
	Lys 305	Leu	Ser	Arg	Pro	Phe 310	Gln	Asn	Gln	Thr	His 315	Ala	Lys	Arg	Ala	Tyr 320
10	Arg	Glu	Leu	Val	Leu 325	Met	Lys	Суз	Val	Asn 330	His	Lys	Asn	Ile	Ile 335	Gly
	Leu	Leu	Asn	Val 340	Phe	Thr	Pro	Gln	Lys 345	Ser	Leu	Glu	Glu	Phe 350	Gln	qaA
	Val	Tyr	Ile 355	Val	Met	Glu	Leu	Met 360	Asp	Ala	Asn	Leu	Cys 365	Gln	Val	Ile
15	Gln	Met 370	Glu	Leu	Asp	His	Glu 375	Arg	Met	Ser	Tyr	Leu 380	Leu	Tyr	Gln	Met
	Leu 385	Cys	Gly	Ile	Lys	His 390	Leu	His	Ser	Ala	Gly 395	Ile	Ile	His	Arg	Asp 400
20		Lys			405					410	-	_			415	
		Aap		420			_		425	_				430		
		Tyr	435					440					445			
25		Gly 450					455					460				•
	465	Glu				470					475					480
30	-	Gln	_		485					490					495	
		Met -	_	500					505	_		_		510		
0.5		Lys	515		-	_		520		-			525			
35		Pro 530		_			535		_		_	540				
	545	Leu			_	550				-	555					560
40		Asp			565					570					575	
		Glu		580					585					590		
AE		Arg	595					600		_			605	-		
45		Met 610 Ser					615		-		GIĀ	620		Arg	GIÀ	GIII
	625		PIO	nen	AIG	630		GIII	GIII							
50			(2	) IN	FORM	OITA	N FO	R SE	Q ID	NO:	46:					
		(			NCE GTH:											

- (A) LENGTH: 1824 base pairs (B) TYPE: nucleic acid
- 55 (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

87

				OLEC EATU		TYPE	: cI	NA									
5			(B)	NAM LOC OTH	ATIC	N: 1	1	821	quen	ice							
10		(×	ci) S	EQUE	NCE	DESC	RIPI	: NOI	SEÇ	ID	NO:4	6:					
									TTC Phe								48
15									GGC Gly 25								96
20		-							GGC Gly							_	144
25									CCC Pro								192
30									AGC Ser								240
00									ATG Met								288
35									GGC Gly 105							_	336
40									GTG Val								384
45									ATC Ile								432
50									ATC Ile								480
Ju									CGC Arg						_		528
55	ana	CNG	CTIC	aca	GNC	CAC	ጥአር	מאמ	מאמ	מתה	אככ	CCC	אינים	ממר	GAC	GGC	576

87

Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly

				180					185					190			
				CTG													624
5	Pro	vaı	195	Leu	Pro	Asp	Asn	200	ıyr	Leu	ser	Thr	205	ser	Ala	Leu	
	AGC	ααα	GAC	CCC	AAC	GAG	AAG	CGC	GAT	CAC	ATG	GTC	CTG	СТС	GAG	ידיני	672
		Lys		Pro		_	Lys					Val					0,2
10		210					215					220					
				GCC													720
	225	inr	Ala	Ala	GIA	230	Thr	ьeu	GIĀ	Met	235	GIU	ьeu	lyr	гÀг	240	
15	GGA	CTC	AGA	TCT	CGA	GGG	AAA	ATG	TCT	CAG	GAG	AGG	CCC	ACG	TTC	TAC	768
				Ser	Arg					Gln					Phe		,
					245					250					255		
20				CTG Leu													816
20	mg	0111	010	260	*****	_,,			265	014	<b>,</b>	110		270	-1-	<b>U</b> 111	
	AAC	CTG	TCT	CCA	GTG	GGC	TCT	GGC	GCC	TAT	GGC	TCT	GTG	TGT	GCT	GCT	864
25	Asn	Leu	Ser 275	Pro	Val	Gly	Ser	Gly 280	Ala	Tyr	Gly	Ser	Val 285	Cys	Ala	Ala	
20			2,5					200					205				
				AAA Lys													912
00		290					295	5				300	-4-			<b>J</b>	
30	CCA	TTT	CAG	TCC	ATC	ATT	CAT	GCG	AAA	AGA	ACC	TAC	AGA	GAA	CTG	CGG	960
		Phe	Gln	Ser	Ile	Ile 310	His	Ala	Lys	Arg	Thr 315	Tyr	Arg	Glu	Leu	Arg 320	
	305					310					213					320	
35				CAT His													1008
					325	•				330		•			335		
		ACA	CCT	GCA	AGG	TCT	CTG	GAG	GAA	TTC	AAT	GAT	GTG	TAT	CTG	GTG	1056
40 .	Phe	Thr	Pro	Ala	_	Ser						_		Tyr 350	Leu	Val	
				ATG Met													1104
45	•		355		-		-	360					365	-		_	
			_	GAC													1152
	Leu	Thr 370	Asp	Asp	His	Val	Gln 375	Phe	Leu	Ile	Tyr	Gln 380	Ile	Leu	Arg	Gly	
50 🕜																	
				ATA Ile													1200
	385	4 -				390		- 4"			395	J	-		•	400	
55	AGT	AAT	CTA	GCT	GTG	AAT	GAA	GAC	TGT	GAG	CTG	AAG	ATT	CTG	GAT	TTT	1248
	Ser	Asn	Leu	Ala	Val	Asn	Glu	Asp	Cys	Glu	Leu	Lys	Ile	Leu	Asp	Phe	

89

				405				410			415		
5	_	_		CAC His	_						_		1296
10				GCT Ala									1344
				ATT Ile									1392
15			_	TTG Leu	_	_			_	_			1440
20				CTC Leu 485									1488
25				TCT Ser		Asn							1536
				TTT									1584
30	_			GAG Glu			_						1632
35				GCC Ala									1680
40				CCA Pro 565									1728
45				ATA Ile				Ser			_	_	1776
En				CCA Pro								TGA	1824
50													

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 607 amino acids
(B) TYPE: amino acid

90

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein 5
  - (v) FRAGMENT TYPE: internal

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

	Met	Val	Ser	Гуs	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu
10	1	~1	<b>.</b>	<b>3</b>	5	<b>3</b>	**- 3	•	<b>-</b> 1	10		-1			15	<b>~</b> 3
	vai	GIU	Leu	20	GIÀ	Asp	vai	Asn	25 25	HIS	гÀа	Pne	ser	30	ser	GIY
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
15	Cys		Thr	Gly	Lys	Leu		Val	Pro	Trp	Pro		Leu	Val	Thr	Thr
	Len	50 Thr	Tyr	Glv	Val	Gln	55 Cvs	Phe	Ser	Δra	Tur	60 Pro	Agn	Hig	Met	Tave
	65		* 7 -	01,	,,,	70	٠,٠			**** 9	75	110	Anp			80
20	Gln	His	qaA	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	qaA	Gly 105	Asn	Tyr	ГÀЗ	Thr	Arg 110	Ala	Glu
	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	Lys	Gly
25	Ile	Asp 130	Phe	Lys	Glu	qaA	Gly 135	Asn	Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr
	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	Asp	Lys	Gln	Lys	Asn
	145					150				_	155		_			160
30	Gly	Ile	Lys	Val	Asn 165	Phe	ГÀЗ	Ile	Arg	His 170	Asn	Ile	Glu	qaA	Gly 175	Ser
	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly
	Pro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200	Tyr	Leu	Ser	Thr	Gln 205	Ser	Ala	Leu
35	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe
		Thr	Ala	Ala	Gly		Thr	Leu	Gly	Met	_	Glu	Leu	Tyr	ГÀв	
	225	T.O.I.	Arg	Car	Arc	230	Tage	Mat	Car	Gln	235	7~~	Pro	ጥb æ	Dhe	240
40	_		_		245	_	-			250		_			255	_
	Arg	Gln	Glu	Leu 260	Asn	Lys	Thr	Ile	Trp 265	Glu	Val	Pro	Glu	Arg 270	Tyr	Gln
	Asn	Leu	Ser 275	Pro	Val	Gly	Ser	Gly 280	Ala	Tyr	Gly	Ser	Val 285	Сув	Ala	Ala
45	Phe	Авр 290	Thr	Lys	Thr	Gly	Leu 295	Arg	Val	Ala	Val	Lys 300	Lys	Leu	Ser	Arg
	Pro	Phe	Gln	Ser	Ile	Ile	His	Ala	Lys	Arg	Thr	Tyr	Arg	Glu	Leu	Arg
	305	_	_			310			_		315		_	_	<b>-</b>	320
50	Leu	Leu	Lys	His	Met 325	Lys	His	Glu	Asn	Val 330	He	GТĀ	Leu	Leu	Asp 335	vaı
	Phe	Thr	Pro	Ala 340	Arg	Ser	Leu	Glu	Glu 345	Phe	Asn	Asp	Val	Tyr 350	Leu	Val
	Thr	His	Leu 355	Met	Gly	Ala	Asp	Leu 360	Asn	Asn	Ile	Val	Lys 365	Сув	Gln	Lys
55	Leu	Thr 370	_	Asp	His	Val	Gln 375	Phe	Leu	Ile	Tyr	Gln 380		Leu	Arg	Gly

	385	Lys	Tyr	Ile	His	Ser 390	Ala	Asp	Ile	Ile	His 395	Arg	Asp	Leu	Lys	Pro	
		Asn	Leu	Ala	Val		Glu	Asp	Cvs	Glu		Lvs	Ile	Leu	Asp		
					405				-2	410		-2			415		
5	Gly	Leu	Ala	Arg 420	His	Thr	Asp	Asp	Glu 425	Met	Thr	Gly	Tyr	Val 430	Ala	Thr	
	Arg	Trp	Tyr 435	Arg	Ala	Pro	Glu	Ile 440	Met	Leu	Asn	Trp	Met 445	His	Tyr	Asn	
10	Gln	Thr 450	Val	Asp	Ile	Trp	Ser 455	Val	Gly	Сув	Ile	Met 460	Ala	Glu	Leu	Leu	
	Thr 465	Gly	Arg	Thr	Leu	Phe 470	Pro	Gly	Thr	Ąsp	His 475	Ile	Asp	Gln	Leu	Lys 480	
		Ile	Leu	Arg	Leu 485	Val	Gly	Thr	Pro	Gly 490		Glu	Leu	Leu	Lys 495		
15	Ile	Ser	Ser			Ala	Arg	Asn	Tyr 505		Gln	Ser	Leu	Thr 510		Met	
	Pro	Lys		500 Asn	Phe	Ala	Asn			Ile	Gly	Ala			Leu	Ala	
	**- 3	B	515	T	<b>a</b> 1	T	Woh	520	1707	Tou	2 000	Com	525	T 140	7~~	Tlo	
20	vai	Asp 530	ьеи	ьеи	GIU	гув	535	ren	vaı	ren	Авр	540	Asp	гув	AIG	116	
	Thr 545	Ala	Ala	Gln	Ala	Leu 550	Ala	His	Ala	_	Phe 555	Ala	Gln	Tyr	His	Asp 560	
		Asp	Asp	Glu	Pro		Ala	Asp	Pro			Gln	Ser	Phe	Glu		
25	<b>3</b>	<b>3</b>	7	T	565	<b>7</b>	<b>a</b> 1	M	T	570	7	mb		N ~	575	1701	
25		Asp		580					585					590		VAI .	
•	Ile	Ser	Phe 595	Val	Pro	Pro	Pro	Leu 600	Asp	Gln	Glu	Glu	Met 605	Glu	Ser		
30			(2)	INI	PORM	OITA	v FOI	SEC	o ID	NO:	48:						
00			\~ /		. 0				~		~~ .						
		(:		EQUEI LENC													
		(:	(A) (B)	LENG	ETH: E: n	290° ucle:	7 bas	se pa	airs								
35		()	(A) (B) (C)	LENG TYPI STR	ETH: E: ni ANDEI	290° icle: DNES	7 bas ic as S: s:	se pa cid ingle	airs		·						
35			(A) (B) (C) (D)	LENG TYPI STRI	ETH:  ANDE	290° ucle: DNESS Y: l:	7 bas ic ac S: s: inea	se pa cid ingle	airs								
35		(:	(A) (B) (C) (D)	LENG TYPI STRI TOPO	TH:  ANDE  OLOGI  CULE	290° ucle: DNESS Y: l:	7 bas ic ac S: s: inea	se pa cid ingle	airs								
35		(:	(A) (B) (C) (D)	LENG TYPI STRI TOPG MOLEG	ETH: E: nv ANDE  OLOG  CULE  URE:	290° icle: DNESS Y: l:	7 basic acic acic acic acic acic acic acic	se pa cid ingle r	airs								
		(:	(A) (B) (C) (D)  Li) !	LENG TYPI STRI TOPG MOLEG FEATU	ETH: E: NAME  ANDE  CULE  URE:  ME/KO	290° Clessoness Y: l: TYPI	7 basic ac S: s: inear E: cl	se paid ingle r ONA	airs	nce							
		(:	(A) (B) (C) (D)  Li) 1 (A) (B)	LENG TYPI STRI TOPG MOLEG	ETH: E: NO ANDEL DLOG CULE URE: ME/KO CATIO	290° Cle: DNESS Y: 1: TYPI EY: 0	7 basic ad S: s: s: sinear Codin	se pacid ingler  ONA  ng Se 2904	airs	nce							
		(:	(A) (B) (C) (D)  Li) ! ix) ! (A) (B)	LENG TYPI STRA TOPG MOLEG FEATU NAI	STH: S: NY ANDER DLOG! CULE URE: ME/KO CATIO	290° icle: DNESS Y: 1: TYPI EY: 0	7 basic ac 5: s: inear E: cl Codin	se pacid ingle r  ONA  ng Se 2904	airs e		NO:	<b>4</b> B:					
40		(; (; ();	(A) (B) (C) (D) (ii) I (A) (B) (D) (A) (A) (B) (D)	LENG TYPI STRA TOPO MOLEG FEATO NAI LOG OTI	GTH: E: NAME  ANDE  CULE  URE:  ME/KO  CATIO  HER  ENCE  GGC	290° icle: ONESS Y: 1: TYPI EY: 0 ON: 1 INFO	7 basic accine a	se partial distribution of the contract of the	airs eque : SE TTC	Q ID ACC	GGG	GTG					48
40	Met	(:	(A) (B) (C) (D) (ii) I (A) (B) (D) (A) (A) (B) (D)	LENG TYPI STRA TOPO MOLEG FEATO NAI LOG OTI	ETH: E: nv ANDEI OLOGI CULE URE: ME/KO CATIO HER ENCE GGC Gly	290° icle: ONESS Y: 1: TYPI EY: 0 ON: 1 INFO	7 basic accine a	se partial distribution of the contract of the	airs eque : SE TTC	Q ID ACC Thr	GGG	GTG			Ile		. 48
40 45		(; (; ();	(A) (B) (C) (D) (ii) I (A) (B) (D) (A) (A) (B) (D)	LENG TYPI STRA TOPO MOLEG FEATO NAI LOG OTI	GTH: E: NAME  ANDE  CULE  URE:  ME/KO  CATIO  HER  ENCE  GGC	290° icle: ONESS Y: 1: TYPI EY: 0 ON: 1 INFO DESG	7 basic accine a	se partial distribution of the contract of the	airs eque : SE TTC	Q ID ACC	GGG	GTG					48
40	Met 1 GTC	(: (: GTG Val	(A) (B) (C) (D)  Li) f (A) (B) (D)  AGC Ser  CTG	LENG TYPI STRI STRI TOPO MOLEG FEATU ) NAI ) LOG ) OTI SEQUI AAG Lys	ETH: E: no ANDED DLOGY CULE URE: ME/KO CATIO HER ENCE GGC Gly 5	290° ucle: DNESS Y: 1: TYPI EY: 0 DN: : INFO DESG GAG GLU GAC	7 basic ac S: s: inear E: cl Codin 1: RMAT CRIP GAG Glu	se picid ingle r DNA ag Se 2904 ION: TION CTG Leu AAC	equer : SE TTC Phe GGC	Q ID ACC Thr 10 CAC	GGG	GTG Val TTC	Val AGC	Pro GTG	Ile 15 TCC	Leu	48
40 45	Met 1 GTC	(: (: GTG Val	(A) (B) (C) (D)  Li) f (A) (B) (D)  AGC Ser  CTG	TYPI STRI STRI STRI STRI STRI STRI STRI STR	ETH: E: no ANDED DLOGY CULE URE: ME/KO CATIO HER ENCE GGC Gly 5	290° ucle: DNESS Y: 1: TYPI EY: 0 DN: : INFO DESG GAG GLU GAC	7 basic ac S: s: inear E: cl Codin 1: RMAT CRIP GAG Glu	se picid ingle r DNA ag Se 2904 ION: TION CTG Leu AAC	equer : SE TTC Phe GGC Gly	Q ID ACC Thr 10 CAC	GGG	GTG Val TTC	Val AGC	Pro GTG Val	Ile 15 TCC	Leu	
40 45 50	Met 1 GTC Val	(; GTG Val GAG Glu	(A) (B) (C) (D)  Li) I (A) (B) (D)  AGC Ser  CTG Leu	TYPI STRI STRI STRI STRI TOPO MOLEO FEAT OF LOO AAG Lys GAC Asp 20	ETH: E: no ANDER CULE URE: ME/KO CATIC HER  GGC Gly GGC Gly	290° ucle: DNESS Y: 1: TYPI EY: 0 ON: 1 INFO DESG GAG Glu GAC Asp	7 basic ac S: s: inear E: cl Codin 1: RMAT GAG Glu GTA Val	se picid ingle r DNA ORS 22904 ION: CTG Leu AAC Aan	equer : SE TTC Phe GGC Gly 25	Q ID ACC Thr 10 CAC His	GGG Gly AAG Lys	GTG Val TTC Phe	Val AGC Ser	GTG Val 30	Ile 15 TCC Ser	GGC Gly	96
40 45	Met 1 GTC Val	(: (: GTG Val	(A) (B) (C) (D) (II) I (A) (B) (D) (A) CO	TYPI STRI STRI STRI STRI HOLE HOLE HOLE HOLE HOLE HOLE HOLE HOLE	ETH: E: NO ANDER CULE URE: ME/KO CATIO HER  GGC Gly GGC Gly GAT	290° icle: DNESS Y: 1: TYPI EY: 0 ON: 1 INFO DESG GAG Glu GAC Asp	7 basic ac S: s: inear E: cl Codin 1: RMAT: GAG Glu GTA Val	se picid ingle r DNA  22904 LON: CTG Leu  AAC Aan	equer : SE TTC Phe GGC Gly 25	Q ID ACC Thr 10 CAC His	GGG Gly AAG Lys	GTG Val TTC Phe	Val AGC Ser	Pro GTG Val 30	Ile 15 TCC Ser	GGC Gly	

								32						
		35				40					45			
5	 -			CTG Leu										192
10	 			CAG Gln 70										240
				AAG Lys										288
15				AAG Lys								_	_	336
20				GAC Asp										384
25	 			GAC Asp										432
				AAC Asn 150										480
30				TTC Phe										528
35				CAC His										576
40				GAC Asp	Asn		Tyr					_		624
45				GAG Glu										672
E0.				ATC Ile 230						Glu				720
50				Ser					Gln				TAT	768
55													GAC Asp	816

			260					265					270			
5	 			•				TTA Leu								864
10								ATT Ile								912
10								TTT Phe								960
15								CCC Pro								1008
20								TCT Ser 345								1056
25								GAT Asp	-							1104
20								ATC Ile								1152
30								CTA Leu								1200
35								CTT Leu								1248
40		Glu	Met	Ile	Asp	Val	His	GTT Val 425	Leu	Ala	Asp	Ala	Phe	Lys		1296
45															AGT Ser	1344
F0		Ile					Glu					Glu			ATT	1392
50	Leu					Ile					Ile				TAT Tyr 480	1440
55															CAA Gln	1488

PCT/DK98/00145 WO 98/45704

										94		•					
					485					490					495		
5				AAA Lys 500										_	_	_	1536
10				CTT Leu													1584
10				TÀ2													1632
15				GCA Ala													1680
20				AAC Asn													1728
25				GGA Gly 580													1776
30				GAC Asp													1824
30				TAT Tyr													1872
35				TTT Phe													1920
40				TCT Ser													1968
45				TAT Tyr 660						Val							2016
50									Val							GCT Ala	2064
50			Lys					Туг					Gln			AGT Ser	2112
55	CGA Arg	GAA Glu	TAT Tyr	GAT Asp	AGA Arg	TTA Leu	TAT	GAA Glu	GAA Glu	TAT Tyr	ACC Thr	CGC Arg	ACA Thr	TCC Ser	CAG Gln	GAA Glu	2160

95

									•	95							
	705					710					715					720	
5	ATC Ile			Lys					Glu								2208
10									CAA Gln 745								2256
10									AAT Asn								2304
15	ATG Met	CAT His 770	AAT Asn	TAT Tyr	GAT Asp	AAG Lys	TTG Leu 775	AAG Lys	TCT Ser	CGA Arg	ATC Ile	AGT Ser 780	GAA Glu	ATT Ile	ATT Ile	GAC Asp	2352
20	AGT Ser 785	AGA Arg	AGA Arg	AGA Arg	TTG Leu	GAA Glu 790	GAA Glu	GAC Asp	TTG Leu	AAG Lys	AAG Lys 795	CAG Gln	GCA Ala	GCT Ala	GAG Glu	TAT Tyr 800	2400
25	CGA Arg	GAA Glu	ATT Ile	GAC Asp	AAA Lys 805	CGT Arg	ATG Met	AAC Asn	AGC Ser	ATT Ile 810	AAA Lys	CCA Pro	GAC Asp	CTT Leu	ATC Ile 815	CAG Gln	2448
	CTG Leu	AGA Arg	AAG Lys	ACG Thr 820	AGA Arg	GAC Asp	CAA Gln	TAC Tyr	TTG Leu 825	ATG Met	TGG Trp	TTG Leu	ACT	CAA Gln 830	AAA Lys	GGT Gly	2496
30	GTT Val	CGG Arg	CAA Gln 835	AAG Lys	AAG Lys	TTG Leu	AAC Asn	GAG Glu 840	Trp	TTG Leu	GGC Gly	AAT Asn	GAA Glu 845	AAC Asn	ACT Thr	GAA Glu	2544
35	GAC Asp	CAA Gln 850	Tyr	TCA Ser	CTG Leu	GTG Val	GAA Glu 855	GAT Asp	GAT Asp	GAA Glu	GAT Asp	TTG Leu 860	CCC	CAT His	CAT His	' GAT Asp	2592
40	GAG Glu 865	Lys	ACA Thr	TGG	AAT Asn	GTT Val 870	Gly	AGC	AGC Ser	AAC Asn	CGA Arg 875	Asn	AAA Lys	GCT Ala	GAA Glu	AAC Asn 880	2640
45	CTG Leu	TTG Leu	CGA Arg	GGG Gly	AAG Lys 885	Arg	GAT Asp	GGC Gly	ACT Thr	Phe	Leu	GTC Val	CGG Arg	GAG Glu	AGC Sei 899	AGT Ser	2688
	AAA Lys	CAG	GGC Gly	TGC Cys 900	Туг	GCC Ala	TGC Cys	TCT	GTA Val	. Val	GTG Val	GAC Asp	GGC Gly	GA# Glu 910	ı Val	A AAG	2736
50	CAT His	TG1	GT( Val	. Ile	AAC ASI	AAA Lys	A AC#	GC Ala 920	a Thr	GGC Gly	TAT	r GGC c Gly	TT: Pho 92!	e Ala	GA(	g CCC	2784
55	TAT Tyr	AA 1 c Asi	TTC 1 Let	TAC	C AGO	C TCT	r CTC	E AA	A GAJ s Glv	A CTO	GTO 1 Va	G CTI Let	A CA'	r TAC	C CA	A CAC n His	2832

96

ACC TCC CTT GTG CAG CAC AAC GAC TCC CTC AAT GTC ACA CTA GCC TAC

Thr Ser Leu Val Gln His Asn Asp Ser Leu Asn Val Thr Leu Ala Tyr

945

950

960

CCA GTA TAT GCA CAG CAG AGG CGA TGA 2907
Pro Val Tyr Ala Gln Arg Arg
965

10

15

930

(2) INFORMATION FOR SEQ ID NO:49:

935

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 968 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- 20 (ii) MOLECULE TYPE: protein
  (v) FRAGMENT TYPE: internal
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:
- 25 Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu

  1 5 10 15

  Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly

20 25 30
Glu Glv Glu Glv Asp Ala Thr Tvr Glv Lvs Leu Thr Leu Lys Phe Ile

Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 30 35 40 45

Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 50 55 60

Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 65 70 75 80

35 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 90 95

Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 100 105 110

Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
40 115 120 125

Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 130 140

Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 145 150 155

45 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 165 170 175

Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
180 185 190

Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 50 205

Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 210 220

Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 225 230 235 240

55 Gly Leu Arg Ser Met Ser Ala Glu Gly Tyr Gln Tyr Arg Ala Leu Tyr 245 250 255

	Asp	Tyr	Lув	Lув 260	Glu	Arg	Glu	Glu	Asp 265	Ile	Ąap	Leu	His	Leu 270	Gly	Asp
	Ile	Leu	Thr 275	Val	Asn	Lys	Gly	Ser 280	Leu	Val	Ala	Leu	Gly 285	Phe	Ser	Asp
5	•	290	Glu		_		295			_	_	300				
	305		Thr			310					315					320
10		_	Arg	_	325					330					335	
	_		Leu	340					345					350		
			Gln 355					360					365			
15		370	Ile				375					380				
	385	-	Gly			390					395					400
20			Ala		405					410					415	
			Glu	420		_			425					430		
	-		Leu 435					440					445			
25		450	Ile				455					460				
	465		Leu			470					475					480
30			Thr	•	485					490					495	
			Ser	500					505					510		
			Met 515					520					525			
35		530	Ile				535					540				
	545		Pro			550					555					560
40			Asn _		565					570					575	
			Trp	580					585					590		
45	_		Ala 595					600					605			
45		610					615					620				
	625		Ile			630					635					640
50			Ser		645					650					655	,
			Gln	660	1				665	;				670	1	
		-	675	i				680	l				685			
55	Val	Gly	Lys	гЛа	ьеи	. н18	GIU		ASI	Thr	GII	700		GIU	гтАв	s se

	705		_			710				Tyr	715					720	
					725					Ala 730					735		
5				740					745	Glu				750			
	Ile	Glu	Lys 755	Phe	Lys	Arg	Glu	Gly 760	Asn	Glu	ГÀв	Glu	Ile 765	Gln	Arg	Ile	
10		770					775			Arg		780					
	785	_	_			790				Lys	795					800	
	_				805					Ile 810					815		
15		_		820					825	Met				830			
		_	835					840		Leu			845				
20	_	850	_				855			Glu		860					
	865	_				870				Asn	875					880	(
			_	_	885					Phe 890					895		
25				900					905					910			
		• -	915					920		Gly			925				
30	_	930					935			Leu		940					
	Thr 945	Ser	Leu	Val	Gln	His 950		Asp	Ser	Leu	Asn 955		Thr	Leu	Ala	Tyr 960	
	Pro	Val	Tyr	Ala	Gln 965	Gln	Arg	Arg									
35			(2	) IN	FORM	ATIO	n FO	R SE	Q ID	NO:	50:						
		(	i) S	EQUE	NCE	CHAR	ACTE	RIST	'ICS :								
40			(B) (C)	TYP STR	GTH: E: n ANDE OLOG	ucle DNES	ic a S: s	cid ingl									
<b>45</b>					CULE URE :		E: c	DNA									
<b>E</b> 0			(E	) LC	ME/K CATI THER	ON:	1	2157	, -	ence							
50		•	(xi)	SEQU	JENCE	DES	CRIE	PTION	1: SI	EQ II	ОИ	:50:					
	Met				Gly											C CTG e Leu	48
55	1				5					TO					د. د		

							99						
			GAC Asp 20										96
5			GGC Gly										144
10			GGC Gly					_		_		_	192
15			GGC Gly	_									240
			TTC Phe										288
20			TTC Phe 100										336
25			GAG Glu			_		_	_				384
30			AAG Lys										432
35			AGC Ser							_			480
			GTG Val								_		528
40			GCC Ala 180										576
45			CTG Leu			Tyr				Ser		CTG Leu	624
50		Asp	CCC						Leu				672
55	Thr				Thr			Glu				TCC Ser 240	720

							100		•				
			TCT Ser										768
5			ACG Thr 260										816
10			GGG Gly										864
15			TGG Trp										912
20			GGA Gly										960
20			ACT Thr									_	1008
25			AGT Ser 340								_		1056
30			TTC Phe										1104
35	_		CGA Arg	_			_	_					1152
40			GAT Asp										1200
40			GCT Ala	Asn	Lys		Asp	Glu					1248
45			CAG Gln 420										1296
50			ACC Thr			Glu							1344
55		Ser	ATT		Thr					Gly		CCA Pro	1392

		TAT Tyr											1440
5		ACA Thr											1488
10		GAA Glu 500											1536
15		CAG Gln											1584
20		TAT Tyr											1632
20		TCA Ser											1680
25		TGC Cys											1728
30		ACA Thr 580											1776
35		GAA Glu											1824
		CCC Pro											1872
40		ATT											1920
45		GCT Ala		Leu				Asn				Ala	1968
50		CTA Leu 660	Thr				Ile				Val	Lys AAA	2016
55		Ala				Gln				Thr		TGC Cys	2064

	TGG .										Gln						2112
5	TTA Leu 705															TAA	2160
10			(2)	INF	ORMA	TION	FOF	SEC	DID	NO : 5	1:						
15		(i	(A) (B) (C)	LENG TYPE STRA	TH: : an ANDEL	HARA 719 nino ONESS	amir ació : si	no ac l ingle	eids								
20		(7	r) FF	LAGME	ent 1	TYPE: TYPE:	int	erna		) ID	NO:5	;1:					
	1			-	5				Phe	10.					15		
25				20					Gly 25					30		•	
		_	35					40	Gly				45				
30	-	50		_	_		55		Pro			60					
	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Сув	Phe	Ser	Arg	Tyr 75	Pro	qaA	His	Met	80 Lys	
		His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu	
35				100					Gly 105					110			
	Val	ГÀЗ	Phe 115	Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	Lys	Gly	
40	Ile	Asp 130	Phe	Lув	Glu	Asp	Gly 135		Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr	
	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	ĄsĄ	Lys	Gln	Lys	Asn 160	
		Ile	Lys	Val	Asn 165	Phe	Lys	Ile	Arg	Нів 170	Asn	Ile	Glu	Asp	Gly 175	Ser	
45	Val	Gln			Asp					Asn					Asp	Gly	
	Pro	Val	Leu 195	Leu		Asp	Asn	His 200	Tyr		Ser	Thr	Gln 205		Ala	Leu	
50	Ser	Lys 210	Asp		Asn	Glu	Lys 219			His	Met	Val 220		Leu	Glu	Phe	
	Val 225	Thr		Ala	Gly	7 Ile 230	Thr			Met	Asp 235		Leu	Туг	Lys	Ser 240	
			Arg	Ser	Arg 245	Ala		ı Ala	. Ser	Asr 250	Ser		Met	. Sez	Sez 255	Ile	
55	Leu	Pro	Phe	Thr 260	Pro		Val	l Val	L Lys 265	Arç		. Leu	Gly	270		. FAs	

	Ser	Ala	Gly 275	Gly	Ser	Gly	Gly	Ala 280	Gly	Gly	Gly	Glu	Gln 285	Asn	Gly	Gln
	Glu	Glu 290		Trp	Суз	Glu	Lys 295	Ala	Val	Lys	Ser	Leu 300	Val	Lys	Lys	Leu
5	Lys 305	Lys	Thr	Gly	Arg	Leu 310	Asp	Glu	Leu	Glu	Lys 315	Ala	Ile	Thr	Thr	Gln 320
		Сув	Asn	Thr	Lys 325	Cys	Val	Thr	Ile	Pro 330	Ser	Thr	Cys	Ser	Glu 335	Ile
10	Trp	Gly	Leu	Ser 340		Pro	Asn	Thr	Ile 345		Gln	Trp	Asp	Thr 350		Gly
	Leu	Tyr	Ser 355		Ser	Glu	Gln	Thr 360		Ser	Leu	Asp	Gly 365	Arg	Leu	Gln
	Val	Ser 370		Arg	Lys	Gly	Leu 375		His	Val	Ile	Tyr 380	Сув	Arg	Leu	Trp
15	Arg 385	Trp	Pro	Asp	Leu	His 390	Ser	His	His	Glu	Leu 395	ГÀЗ	Ala	Ile	Glu	Asn 400
	Сув	Glu	Tyr	Ala	Phe 405	Asn	Leu	Lys	Lys	Asp 410	Glu	Val	Сув	Val	Asn 415	Pro
20	Tyr	His	Tyr	Gln 420	Arg	Val	Glu	Thr	Pro-	Val	Leu	Pro	Pro	Val 430	Leu	Val
	Pro	Arg	His 435	Thr	Glu	Ile	Leu	Thr 440	Glu	Leu	Pro	Pro	Leu 445	Asp	Asp	Tyr
	Thr	His 450	Ser	Ile	Pro	Glu	Asn 455	Thr	Asn	Phe	Pro	Ala 460	Gly	Ile	Glu	Pro
25	Gln 465	Ser	Asn	Tyr	Ile	Pro 470	Glu	Thr	Pro	Pro	Pro 475	Gly	Tyr	Ile	ser	Glu 480
•	Asp	Gly	Glu	Thr	Ser 485	Asp	Gln	Gln	Leu	Asn 490	Gln	Ser	Met	Asp	Thr 495	Gly
30	Ser	Pro	Ala	Glu 500	Leu	Ser	Pro	Thr	Thr 505	Leu	Ser	Pro	Val	Asn 510	His	Ser
	Leu	Asp	Leu 515	Gln	Pro	Val	Thr	Tyr 520	Ser	Glu	Pro	Ala	Phe 525	Trp	Сув	Ser
		Ala 530	_	_			535					540				
35	545	Gln				550					555					560
		Arg			565					570					575	
40		Glu		580					585					590		
		Gly	595					600					605			
		Gln 610					615					620				
45	625					630					635					Gln 640
					645					650	)				655	
50				660					665					670		Гув
			675					680	)				685	i		Cys
		690	)				695	;				700	)			Val
55	Let 705	Thr	Gln	Met	: Gly	710		Ser	· Val	. Arg	715		ser	. Met	. ser	

104

•			(2)	INE	ORMA	TION	FOR	SEÇ	) ID	NO : 5	2:						
5		(i	(A) (B) (C)	LENG TYPE STRE	ICE OF TH: I: nu INDEL OLOGY	2421 clei NESS	bas c ac : si	e pa id ngle	irs								
10		-	•	OLEC	ULE IRE:	TYPE	: cI	AN									
15			(B)	LOC	ME/KE CATIO MER I	N: 1	2	418	quen	ce							
		(з	ci) S	EQUE	ENCE	DESC	RIPI	'ION :	SEÇ	ID.	NO:5	2:					
20		GTG Val															48
25		GAG Glu															96
20		GGC Gly															144
30		ACC Thr 50															192
35		ACC Thr															240
40		CAC His														_	288
45		ACC Thr									-						336
50		AAG Lys				_		_					_				384
-		GAC Asp 130															432
55	AAC	TAC	AAC	AGC	CAC	AAC	GTC	TAT	ATC	ATG	GCC	GAC	AAG	CAG	AAG	AAC	480

Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn

	145				150				155				160	
5			GTG Val									_		528
10			GCC Ala 180											576
			CTG Leu											624
15			CCC Pro											672
20			GCC Ala											720
25		-	TCT Ser											768
30			ATT Ile 260											816
30			AGT Ser											864
35			AGA Arg											912
40			TTG Leu											960
45			AAA Lys		Val				Thr				Leu	-1008
F0				Arg				His				Arg	CTC Leu	1056
50			Pro				Asn				Val		TAT	1104
55													CCA Pro	1152

	370			375			380			
5			CGA Arg							1200
10			AAT Asn 405							1248
			GAG Glu							1296
15			CAG Gln							1344
20			GCT Ala							1392
25	_		CCC Pro						Pro	1440
30	_		GGC Gly 485	_						1488
			GGA Gly							1536
35			AAC Asn							1584
40		_	AAT Asn							1632
45			CCG Pro							1680
50			CAG Gln 565							1728
			GCT Ala							1776
55			TCA Ser							1824

107

									107							
			595					600				605				
5				GGA Gly	_					_	_					1872
10				GAA Glu												1920
,,,				GAA Glu								_				1968
15				GCG Ala 660												2016
20				CCT Pro										_		2064
25				TTT Phe												2112
30				GCA Ala	_						_	_	_	_		2160
				CCT Pro						Gly				_	_	2208
35				GCT Ala 740												2256
40				AGG Arg			_				_				CCA Pro	2304
45			Ser	ATC Ile				Pro				Ile			CAC His	2352
50	Arg 785	Ala					Asp				Thr				GCA Ala 800	2400
	GAC			CCT Pro		Asp		•								2421

55

# (2) INFORMATION FOR SEQ ID NO:53:

```
(i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 806 amino acids
              (B) TYPE: amino acid
5
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: protein
            (v) FRAGMENT TYPE: internal
10
            (xi) SEQUENCE DESCRIPTION: SEO ID NO:53:
     Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
15
      Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
                                      25
     Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
                               40
      Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
20
      Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
                         70
      Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                     85
                                         90
25
      Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
                  100
                                      105
      Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
                                  120
      Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
30
                             135
                                                 140
      Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
                         150
                                             155
      Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                     165
                                        170
                                                             175
35
      Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
                                     185
                                                         190
      Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
                                  200
      Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
40
                                                  220
      Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
                          230
                                              235
      Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Asn Ser Thr Met Asp
                      245
                                          250
45
      Asn Met Ser Ile Thr Asn Thr Pro Thr Ser Asn Asp Ala Cys Leu Ser
                                      265
      Ile Val His Ser Leu Met Cys His Arg Gln Gly Gly Glu Ser Glu Thr
                                  280
                                                      285
      Phe Ala Lys Arg Ala Ile Glu Ser Leu Val Lys Lys Leu Lys Glu Lys
50
                              295
                                                  300
      Lys Asp Glu Leu Asp Ser Leu Ile Thr Ala Ile Thr Thr Asn Gly Ala
                          310
                                             315
      His Pro Ser Lys Cys Val Thr Ile Gln Arg Thr Leu Asp Gly Arg Leu
                      325
                                         330
      Gln Val Ala Gly Arg Lys Gly Phe Pro His Val Ile Tyr Ala Arg Leu
55
                  340
                                      345
```

	Trp	Arg	Trp 355	Pro	Asp	Leu	His	Lys 360	Asn	Glu	Leu	ГÀв	His 365	Val	Lys	Tyr
	Сув	Gln 370	Tyr	Ala	Phe	Asp	Leu 375	Lys	Cys	Asp	Ser	Val 380	Сув	Val	Asn	Pro
5	Tyr 385	His	Tyr	Glu	Arg	Val 390	Val	Ser	Pro	Gly	Ile 395	Asp	Leu	Ser	Gly	Leu 400
	Thr	Leu	Gln	Ser	Asn 405	Ala	Pro	Ser	Ser	Met 410	Met	Val	ГÀв	Asp	Glu 415	Tyr
10	Val	His	Asp	Phe 420	Glu	Gly	Gln	Pro	Ser 425	Leu	Ser	Thr	Glu	Gly 430	His	Ser
	Ile	Gln	Thr	Ile	Gln	His	Pro	Pro 440	Ser	Asn	Arg	Ala	Ser 445	Thr	Glu	Thr
	Tyr	Ser 450	Thr	Pro	Ala	Leu	Leu 455	Ala	Pro	Ser	Glu	Ser 460	Asn	Ala	Thr	Ser
15	Thr		Asn	Phe	Pro	Asn		Pro	Val	Ala	Ser		Ser	Gln	Pro	Ala
	465					470					475					480
	Ser	Ile	Leu	Gly	Gly 485	Ser	His	Ser	Glu	Gly 490	Leu	Leu	Gln	Ile	Ala 495	Ser
20	Gly	Pro	Gln	Pro 500	Gly	Gln	Gln	Gln	Asn 505	Gly	Phe	Thr	Gly	Gln 510	Pro	Ala
	Thr	Tyr	His 515	His	Asn	Ser	Thr	Thr 520	Thr	Trp	Thr	Gly	Ser 525	Arg	Thr	Ala
	Pro	Tyr 530	Thr	Pro	Asn	Leu	Pro 535	His	His	Gln	Asn	Gly 540	His	Leu	Gln	His
25	His 5 <b>4</b> 5	Pro	Pro	Met	Pro	Pro 550	His	Pro	Gly	His	Tyr 555	Trp	Pro	Val	His	Asn 560
	Glu	Leu	Ala	Phe	Gln 565	Pro	Pro	Ile	Ser	Asn 570	His	Pro	Ala	Pro	Glu 575	Tyr
30	Trp	Cys	Ser	Ile 580	Ala	Tyr	Phe	Glu	Met 585	Asp	Val	Gln	Val	Gly 590	Glu	Thr
	Phe	Lys	Val 595	Pro	Ser	Ser	Cys	Pro 600	Ile	Val	Thr	Val	Asp 605	Gly	Tyr	Val
	_	610	Ser	_			615		_		_	620				
35	625		Thr			630					635					640
			Leu		645					650					655	
40			His	660					665	-	•		_	670		
	_		Ala 675		_	_		680		_		_	685			_
		690	Val				695					700				
45	705		Thr			710					715					720
			Ile		725					730					735	
50			Ser -	740			_		745		_	-		750		
			Leu 755					760					765			
	_	770			-		775		_	_		780				
55	Arg 785		Leu	GID	ren	Leu 790		Glu	Val	Leu	His 795	Thr	Met	Pro	Ile	Ala 800

#### Asp Pro Gln Pro Leu Asp 805

			(2)	INF	ORMA	TION	FOR	SEQ	ID	NO : 5	4:						
5		(i	•			HARA 3120											
						clei											
10			•			NESS : li		_									
10			(D)	IOPO	nogi		near										
						TYPE	: cD	AN									•
		(1	.X) £	'EA'TU	RE:												
15					•	Y: C		_	quen	ce							
						N: 1 NFOR											
		_															
20		к)	:i) S	EQUE	INCE	DESC	RIPI	TON:	SEC	i TD	NO:5	4:					
						GAG											48
	Met 1	Val	Ser	Lys	G1y 5	Glu	GIT	Leu	Pne	Thr 10	GIÀ	vaı	vaı	Pro	11e	ren	
																	0.5
25						GAC Asp											96
				20		_			25		•			30		_	
	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	CTG	ACC	CTG	AAG	TTC	ATC	144
30	Glu	Gly		Gly	Asp	Ala	Thr		Gly	Lys	Leu	Thr		гла	Phe	Ile	
			35					40					45				
						CTG											192
35	Сла	Thr 50	Thr	Gly	ГАв	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Vai	Thr	Thr	
00							-										
						CAG Gln											240
	65	7.1.L	-7-	<b>U.</b> .,	•	70	-,-				75					80	
40	ראם	רא ר	GAC	بابليمل	שיים. ה	AAG	ייירר	GCC	АТС	כככ	AAD	GGC	TAC	GTC	CAG	GAG	288
						Lys									Gln		-
					85					90					95		
45						AAG											336
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	qaA	Gly 105	Asn	Tyr	Lys	Thr	Arg	Ala	Glu	
50						GAC Asp											384
JU	val	пЛя	115		СТΆ	rap	****	120			9		125		-, -	1	
	<u>አ</u> ጥር	מאת	ب√بليك	ששמ	Gya	GAC	ממר	אאר	<b>ል</b> ሞር	Carca	GGG	CAC	ממ	ርጥር	GAG	TAC	432
						Asp											
55		130					135					140	•				

							111							
		AGC Ser	_								_			480
5		GTG Val					_		_	_		_		528
10		GCC Ala 180											_	576
15		CTG Leu								_				624
20		CCC Pro							_			_	_	672
20		GCC Ala		_					_					720
25		TCT Ser											_	768
30		CTG Leu 260												816
35		CGG Arg									_			864
40		GAC Asp										_		912
40		GGC												960
45		GAT Asp						ГÀЗ						1008
50		CAG Gln 340					Cys					Val		1056
55						Glu					Arg		GCC Ala	1104

•							112						
•					_	_		_		_	ATG Met	_	1152
5											CTG Leu		1200
10											CAG Gln		1248
15				_							CAG Gln 430		1296
20											GAG Glu		1344
	 										CGT Arg		1392
25											CAC His		1440
30											GAT Asp	_	1488
35											GGC Gly 510		1536
40										_	AAG Lys	_	1584
										_	GAG Glu		1632
45	Gln				Pro				Glu		CTG Leu		1680
50				Thr							ACC Thr	_	1728
55			Lys				Val				CAG Gln 590		1776

				ACC Thr									1824
5				CCC Pro									1872
10				CTT Leu									1920
15				AAC Asn									1968
20			_	CAC His 660	_					_		_	2016
20				GGT Gly									2064
25				CAG Gln									2112
30				TCC Ser									2160
35	_			ACG Thr							_		2208
4.0	_		_	CCA Pro 740	_	_	_				_		2256
40		_	_	CTC Leu						_			2304
45				AAG Lys									2352
50		Ser		AGC Ser									2400
55				AAC Asn					Trp				2448

									114						
								GTG Val 825							2496
5	_			_	-	_		GGT Gly							2544
10								GAC Asp							2592
15				_	_			ACC Thr							2640
20								AAA Lys							2688
								CTG Leu 905							2736
25		_	_					GAT Asp	_	_	_				2784
30			_	_		_	_	GAT Asp					_	_	2832
35								AAT Asn							2880
40								GCC Ala							2928
40	_	_						CAG Gln 985				_			2976
45						Leu		GAG Glu			Asp				3024
50	Val		Glu		Arg		Pro	ATG Met		Ser				CTC Leu	3072
55		Pro		Gly		Phe		TCT	Ala		Gly		Ser	TGA 1	3120

55

115

#### (2) INFORMATION FOR SEQ ID NO:55:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1039 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- 10 (ii) MOLECULE TYPE: protein
  - (v) FRAGMENT TYPE: internal

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

			-														
15	. 1	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
		Val			20	Gly				25					30		
20	)			35		Ąsp			40					45			
		_	50			Lys		55					60				
		65		_		Val	70					75					80
25						Phe 85					90					95	
		_			100	Phe				105					110		
30	)		_	115		Gly			120					125			
			130			Glu		135					140				
		145	_			His	150					155					160
35		_				Asn 165					170					175	
					180	Asp				185					190		
40	0			195		Pro			200					205			
			210			Asn		215					220				
		Val 225	Thr	Ala	Ala	Gly	Ile 230		Leu	Gly	Met	Asp 235		Leu	Tyr	Lys	Ser 240
4	5	Gly				Thr 245	Met	Ala			250	Gln	Ala			255	
					260					265					270		Pro
5	0			275					280					285			Trp
			290					295	;				300	•			Gln
		Leu 305	,			Leu	Val 310	)				315	;				Gln 320
									<b>T</b>								

335

Val Gly Glu Asp Gly Phe Leu Leu Lys Ile Lys Leu Gly His Tyr Ala

325

	Thr	Gln	Leu	Gln 340	ГÀЗ	Thr	Tyr	Asp	Arg 345	Сув	Pro	Leu	Glu	Leu 350	Val	Arg
	Cys	Ile	Arg 355	His	Ile	Leu	Tyr	Asn 360	Glu	Gln'	Arg	Leu	Val 365	Arg	Glu	Ala
5	Asn	Asn 370	Сув	Ser	Ser	Pro	Ala 375	Gly	Ile	Leu	Val	Asp 380	Ala	Met	Ser	Gln
	Lys 385	His	Leu	Gln	Ile	Asn 390	Gln	Thr	Phe	Glu	Glu 395	Leu	Arg	Leu	Val	Thr 400
10	Gln	Asp	Thr	Glu	Asn 405	Glu	Leu	Lys	Lys	Leu 410	Gln	Gln	Thr	Gln	Glu 415	Tyr
			Ile	420		•			425					430		
			Ala 435					440					445			
15		450	Gln				455					460				
	465		Leu			470					475		_			480
20			Gln		485					490					495	
			Gln	500	-	_	_		505			-		510	•	
05			Gly 515					520					525			
25		530	Ile				535					540				
	545		Gln			550		_		•	555					560
30			Ile		565					570					575	
			Ala	580	_				585			-		590		-
35			595 Pro					600					605			
00		610	Leu				615					620				
	625		Asn			630					635		_		_	640
40			Ala		645					650					655	
			Arg	660					665	•	_			670		-
45			675 Ser					680					685			
		690	Leu				695					700				
	705		Ala			710					715		_			720
50			Val		725					730					735	
			Ala	740					745					750		
55			755 Thr					760					765			
	-	770		-		_	775				_	780	-4 ·			

	Asn 785	Ser	Ser	Ser	His	Leu 790	Glu	Asp	Tyr	Ser	Gly 795	Leu	Ser	Val	Ser	Trp 800		
		Gln	Phe	Asn	Arq		Asn	Leu	Pro	Gly		Asn	Tyr	Thr	Phe			
					805					810	•		•		815	-		
5	Gln	Trp	Phe	Asp 820	Gly	Val	Met	Glu	Val 825	Leu	ГÀЗ	Lys	His	His 830	ŗàs	Pro		i
	His	Trp	Asn 835	Авр	Gly	Ala	Ile	Leu 840	Gly	Phe	Val	Asn	Lys 845	Gln	Gln	Ala		
10	His	Asp 850	Leu	Leu	Ile	Asn	Lys 855	Pro	Asp	Gly	Thr	Phe 860	Leu	Leu	Arg	Phe		
	Ser 865	Asp	Ser	Glu	Ile	Gly 870	Gly	Ile	Thr	Ile	Ala 875	Trp	Lys	Phe	qaA	Ser 880		
			_	Asn	885	_			_	890					895			
15	Ser	Ile	Arg	Ser 900	Leu	Ala	Asp	Arg	Leu 905	Gly	Asp	Leu	Ser	Tyr 910	Leu	Ile		
	-		915	Pro	_	_		920	_				925	_	-	_		
20		930		Leu			935					940						
	945			Val		950					955		_			960		
				Thr	965		_			970				_	975			
25				Tyr 980			-		985			_		990		_		
		_	995	Glu		_	:	1000					1005					
30	:	1010		Leu		- :	1015			_		1020	_		_	Leu		
	925	Pro	Pro	Ala	_	Leu 1030	Phe	Thr	ser		Arg L035	GIY	ser	Leu		1		
25			(2)	) INI	ORM!	ATIO	v FO	R SE	O ID	NO:	56:							
35		(:		EQUE														
			(B)	TYP	3: n	ucle	ic a	cid										
40	٠			TOP				_	e		_							
		_		MOLE		TYP	E: c	DNA										
45			(B	) NAI ) LO	CATI	ON:	1	1872	_	nce								
		(-		SEQU						O TD	NO:	56:						
50			,			220				¥								
																AGG	48	
	Met 1	АТА	Ala	ATS	AIA 5	ATS	ΑΙΑ	Pro	GIA	10 GLY	стА	стА	атЪ	GIU	15	Arg		
55																GTG Val	96	
	σ±y		4.1.0	·y	- 41		110	, vai	· val	110	Cry		w.	u				117

							110							
			20			25					30			
5				GAT Asp									144	
10				TAC Tyr									192	
				GCC Ala 70									240	
15				ACG Thr									288	
20				ATA Ile									336	
25				GAT Asp									384	
30				CTT Leu									432	
30				CAG Gln 150									480	
35				CGG Arg									528	
40				AAG Lys									576	
45			His	CAC His		Phe		_	_		Val	 ACA Thr	624	
50		Туг								Lys		ACC	672	
50	Ser				Ser				Lev			CTC Leu 240	720	
55												AAC Asn	. 768	118

								119					
				245				250			255		
5			_	_	TTG Leu	_							816
10	 _				GCC Ala								864
		_	_		GCC Ala								912
15					CGG Arg 310			Phe				_	960
20			_	_	CTG Leu								1008
25					GTG Val								1056
					AAG Lys					_	_	_	1104
30					CCA Pro								1152
35		_	_		CTT Leu 390							GAA Glu 400	1200
40					AAT Asn							GGT Gly	1248
45					TAC Tyr								1296
50												ACT Thr	1344
50		Val			TTT Phe							CAT His	1392
55												ACT Thr	1440

•																			
	465					470					475					480			
	ATA	TTT	TAC	AAA	GAT	GAC	GGG	AAC	TAC	AAG	ACA	CGT	GCT	GAA	GTC	AAG		1488	
E	Ile	Phe	Tyr	Lys	_	Asp	Gly	Asn	Tyr	-	Thr	Arg	Ala	Glu		Lys			
5					485					490					495				
				GAT														1536	
	Pne	GIU	GIY	qaA 500	THE	Leu	vaı	ABII	505	TTE	GIU	ьец	пув	510	116	жър			
10	mmm		<b>~~</b>	C N TO	CCI	220	3.00	amm.	<b>~~</b>	ana	222	» ma	<b>777</b>	m» C	አጸጥ	ጥለጥ		1584	
				GAT Asp														1364	
			515					520					525						
15	AAC	TCA	CAT	AAT	GTA	TAC	ATC	ATG	GCA	GAC	AAA	CCA	AAG	AAT	GGC	ATC		1632	
	Asn	Ser 530	His	Asn	Val	Tyr	Ile 535	Met	Ala	Asp	Lys	Pro 540	Lys	Asn	Gly	Ile			
20				TTC Phe														1680	
	545				•	550					555	•				560			
	TTA	GCA	GAC	CAT	TAT	CAA	CAA	AAT	ACT	CCA	ATT	GGC	GAT	GGC	CCT	GTC		1728	
ae	Leu	Ala	Asp	His		Gln	Gln	Asn	Thr		Ile	Gly	Asp	Gly	Pro 575	Val		•	
25					565					570					3/3				
				GAC Asp														1776	
	пел	Leu	PIO	580		птв	TYL	neu	585	IIIL	GIII	561	ALU	590		2,5			
30	СРТ	ממר	אאר	GAA	DAG	AGA	ርልጥ	ראַר	ATG	איזירי	باسات	ההה	GAG	ጥጥ	GTA	ACA		1824	
			Asn	Glu									Glu	_					
			595					600					605						
35																GAG	T	1873	
	Ala	A1a 610		Ile	Thr	His	615	Met	Asp	GIu	Leu	1yr 620		Pro	GII	GIU			
																		1875	
40	AA										٠							10,5	
			(2	) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	57:								
		(	i) s	EQUE	NCE	CHAR	ACTE	RIST	ICS:										
45				LEN					cids	1									
			(C)	STR	ANDE	DNES	ន: ន	ingl	e										
			(D)	TOP	OLOG	X: T	ınea	.r											
50				MOLE					_									•	
50		,	V) E	RAGM	ENT	TABE	: ın	tern	laı										
		(	(xi)	SEQU	ENCE	DES	CRIF	MOIT	: SE	Q II	NO:	57:							
		: Ala	ı Ala	. Ala		Ala	Ala	Pro	Gly			/ Gly	gly	glı		Arg	•		
55	1 Glv	r Thi	. Ala	i Glv	5 ′Val	. Val	. Pro	Val	[ Val	10 L Pro		/ Glı	ı Val	l Gli	15 1 Val	l Val			
	1			_ ~-1							,		3-						1

				20					25					30		
	Lys	Gly	Gln 35	Pro	Phe	qaA	Val	Gly 40	Pro	Arg	Tyr	Thr	Gln 45	Leu	Gln	Tyr
5	Ile	Gly 50	Glu	Gly	Ala	Tyr	Gly 55	Met	Val	Ser	Ser	Ala 60	Tyr	Asp	His	Val
	Arg 65	ГÀа	Thr	Arg	Val	Ala 70	Ile	Lys	Lys	Ile	Ser 75	Pro	Phe	Glu	His	Gln 80
	Thr	Tyr	Сув	Gln	Arg 85	Thr	Leu	Arg	Glu	Ile 90	Gln	Ile	Leu	Leu	Arg 95	Phe
10	Arg	His	Glu	Asn 100	Val	Ile	Gly	Ile	Arg 105	Asp	Ile	Leu	Arg	Ala 110	Pro	Thr
			115	Met	_	_		120				_	125			
15		130		Lys			135					140				
	145			Leu		150					155					160
				Leu	165	_	_		-	170					175	
20			_	Asp 180		_		_	185		-			190		
			195	His				200					205			
25		210		Arg			215					220			•	
	225			Asp		230			-		235					240
30				Pro	245					250					255	
30				Gly 260 Met					265					270		
			275	Ala				280	_				285			
35		290		Leu			295					300				
	305			Glu		310					315			-	_	320
40				Glu	325					330	•				335	
				340 Leu					345					350		
			355	Phe				360					365			
45		370		Glu			375					380				
	385					390			_		395					400
				Asp	405					410					415	
50				Ala 420					425					430		
			435	Leu				440					445			
55		450		Gln			455					460				
	Asp	Phe	Phe	ГÀв	ser	Ala	Met	Pro	Glu	Gly	Tyr	Val	Gln	Glu	Arg	Thr

										-								
	465					470					475					480		
	Ile	Phe	Tyr	Lys	Asp 485	Asp	Gly	Asn	Tyr	Lys 490	Thr	Arg	Ala	Glu	Val 495	Lys		
5	Phe	Glu	Gly	Asp 500	Thr	Leu	Val	Asn	Arg 505	Ile	Glu	Leu	Lys	Gly 510	Ile	Asp		
	Phe	Lys	Glu 515	Asp	Gly	Asn	Ile	Leu 520	Gly	His	Lys	Met	Glu 525	Tyr	Asn	Tyr		
	Asn	Ser 530		Asn	Val	Tyr	Ile 535		Ala	Asp	Lys	Pro 540		Asn	Gly	Ile		
10	Lys 545		Asn	Phe	Lys	Ile 550		His	Asn	Ile	Lys 555	_	Gly	Ser	Val	Gln 560		
		Ala	qaA	His			Gln	Asn	Thr			Gly	qaA	Gly				
	Leu	Leu	Pro	Asp	565 Asn	His	Tyr	Leu		570 Thr	Gln	Ser	Ala		575 Ser	Lys		
15	Asp	Pro	Asn	580 Glu	Lys	Arg	Asp	His	585 Met	Ile	Leu	Leu	Glu	590 Phe	Val	Thr		
	Ala	Ala	595 Gly	Ile	Thr	His	Gly	600 Met	Asp	Glu	Leu	Tyr	605 Lys	Pro	Gln	Glu		
20		610					615					620						
			(2)	) INI	PORM	ATIOI	v FO	R SE	Q ID	NO:	58:							
		(:		LENC														
25			(B)	TYPI	3: n	ucle	ic a	cid										
•				TOP				-										
30			. :	MOLE FEAT		TYP	E: c	DNA										
		``		) NAI		ev.	Codi	na S	amiai	n.ce								
			(B	) LO	CATI	ON:	1	1811	eque	iice	•							
35		t.		OTI					. 65	0 TD	MO.	co.						
				SEQU									000	999	ana	ama	40	•
				Ala	Ala					Glu					Gln	GTG Val	48	•
40	1				5					10					15			
				GGG Gly													96	5
45				20					25					30				
																CGA Arg	144	ŀ
	ALG	LYL	35	Mec	VAL	Cys	Ser	40	-7-	rsp	F1131.1	. LCG	45	n, n	•			
50																CAG	192	2
	Val	Ala 50	Ile	Lys	ГЛЗ	Ile	Ser 55	Pro	Phe	Glu	His	Gln 60	Thr	Tyr	Cys	Gln		
																AAC	240	0
55	Ar <u>c</u> 65	Thr	Leu	Arg	Glu	11e 70	Lys	Ile	Leu	Lev	75	y Phe	Arg	His	Glu	Asn 80		
																		12

	ATC Ile	ATC Ile	GGC Gly	ATC Ile	AAT Asn 85	GAC Asp	ATC Ile	ATC Ile	CGG Arg	GCA Ala 90	CCA Pro	ACC Thr	ATT Ile	GAG Glu	CAG Gln 95	ATG Met	288
5																	
								GAC									336
	Lys	Asp	۷al	Tyr	Ile	Val	Gln	Asp	Leu	Met	Glu	Thr	Asp	Leu	Tyr	Lys	
				100				-	105					110	-	_	
10								AGC									384
	Leu	Leu	Lys	Thr	Gln	His	Leu	Ser	Asn	qaA	His	Ile	Cys	Tyr	Phe	Leu	
			115					120					125				
	TAT	CAG	ATC	CTG	AGA	GGA	TTA	AAG	TAT	ATA	CAT	TCA	GCT	AAT	GTT	CTG	432
15	$ ext{Tyr}$	Gln	Ile	Leu	Arg	Gly	Leu	Lys	Tyr	Ile	His	Ser	Ala	Asn	Val	Leu	
		130					135					140					
								AAC									480
	His	Arg	Asp	Leu	Lys	Pro	Ser	Asn	Leu	Leu	Leu	Asn	Thr	Thr	Cys	Asp	
20	145					150					155					160	
								CTT									528
	Leu	ГÀв	Ile	Сув	Asp	Phe	Gly	Leu	Ala	Arg	Val	Ala	Asp	Pro	qaA	His	
					165					170					175		
25																	
								GAG									576
	Asp	His	Thr		Phe	Leu	Thr	Glu	Tyr	Val	Ala	Thr	Arg	Trp	Tyr	Arg	
				180					185					190			
30	_		-	-				TCC									624
	Ala	Pro		Ile	Met	Leu	Asn	Ser	Lys	Gly	Tyr	Thr	Lys	Ser	Ile	Asp	
			195					200					205				
25								CTG									672
35	Tie		ser	vaı	GIY	Сув		Leu	Ата	GIU	met		ser	Asn	Arg	Pro	
		210					215					220					
	אייכי	חתים	CCN	003	220	CAT	ma c	Cmm	~~~		ama		~~	3.00	ama	acm.	700
								CTT Leu									720
40	225	PHE	PIG	GIY	гуя		ığı	ьец	Asp	GIII		nea	HTB	116	ren	-	
70	443					230					235					240	
	יוייני	للملكمات	aan	ינויריווי	CC3	m/1%	C2.C	GAA	C B M	ama	3 3 M	mam	n ma	2002	220	mwn a	7.0
																	768
	TIC	Lieu	Gry	aer	245	SET	GIII	Glu	web		ASII	Cys	TIE	116		Leu	
45					443					250					255		
40	222	COT	אכא	አአሮ	ጥለጥ	באתים	CTPT	TCT	CTC	ccc		***	ידיאת	מממ	ore	ccc	816
								Ser									910
	Бyв	ALG	AL 9	260	TAT	neu	Deu	SEL	265	PLO	UTS	цув	ASII	270	Val	FIO	
				200					203					270			
50	TGG	AAC	AGG	ጥጥር፤	יויייר	CCA	AAC	GCT	GAC	<b>דר</b> כ	מממ	GCT	СТС	GAT	ጥጥል	CTG	864
~ <del>-</del>								Ala									001
			275		~			280	بردد		-70		285	<u>P</u>	u		
								~ ~ ~ ~									
	GAT	AAA	ATG	TTG	ACA	TTT	AAC	CCT	CAC	AAG	AGG	ATT	GAA	GTT	GAA	CAG	912
55								Pro									
	•	290					295			, -		300					

									CAG Gln								960
5																	
J					_		_		TTT Phe			_					1008
10									ATT Ile 345								1056
	CAG	CCA	CCA	TAC	AGA	יייטיי	ATG	СУТ	CCA	CCG	GTC	GCC	ACC	ATG	GTG	AGC	1104
15									Pro								
	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	GTC	GAG	CTG	1152
20									Val			_					
	GAC	GGC	GAC	GTA	AAC	GGC	CAC	AAG	TTC	AGC	GTG	TCC	GGC	GAG	GGC	GAG	1200
25									Phe								
	GGC	GAT	GCC	ACC	TAC	GGC	AAG	CTG	ACC	CTG	AAG	TTC	ATC	TGC	ACC	ACC	1248
-	Gly	Asp	Ala	Thr	Tyr 405	Gly	ГÀв	Leu	Thr	Leu 410	ГÀв	Phe	Ile	Cys	Thr 415	Thr	
30	GGC	AAG	CTG	CCC	GTG	CCC	TGG	CCC	ACC	CTC	GTG	ACC	ACC	CTG	ACC	TAC	1296
									Thr 425						_		
	GGC	GTG	CAG	TGC	TTC	AGC	CGC	TAC	CCC	GAC	CAC	ATG	AAG	CAG	CAC	GAC	1344
35	Gly	Val	Gln 435	Cys	Phe	Ser	Arg	Tyr 440	Pro	Asp	His	Met	Lys 445	Gln	His	Asp	
	TTC	TTC	AAG	TCC	GCC	ATG	CCC	GAA	GGC	TAC	GTC	CAG	GAG	CGC	ACC	ATC	1392
40	Phe	Phe 450	ГÀВ	Ser	Ala	Met	Pro 455	Glu	Gly	Tyr	Val	Gln 460	Glu	Arg	Thr	Ile	
																TTC	1440
	Phe	Phe	Lys	Asp	Asp	Gly	Asn	Tyr	Lys	Thr	Arg	Ala	Glu	Val	Lys	Phe	
	465					470					475					480	
45																	1400
									ATC Ile							_	1488
		•	_		485					490					495		•
50																AAC	1536
	Lys	Glu	. Asp	Gly 500		Ile	Leu	Gly	His 505		Leu	Glu	Туг	510		Asn	
															_	AAG	1584
55	Ser	His	Asn 515		Туг	·Ile	: Met	520	_	Lys	Gln	r Lys	525		Ile	. Lys	

PCT/DK98/00145 WO 98/45704

125

5		AAC Asn 530															1632
Ü		GAC Asp								Ile							1680
10		CCC Pro															1728
15		AAC Asn															1776
20		GGG Gly											AATE				1815
			(2)	INI	FORM	ATION	1 FOI	R SEC	O ID	NO:5	59:			-			
25		· (±	(B)	LENC TYPI STRA	GTH: G: ar ANDEI	604 mino ONES	amii acio 3: s:	no ao i ingle	cids								
30		•	ii) M	OLE	CULE		E: p:	rote									
or.			v) FI xi) S							Q ID	ΝΟ:	59:					
35	Met 1	Ala	Ala	Ala	Ala 5	Ala	Ala	Gly	Pro	Glu 10	Met	Val	Arg	Gly	Gln 15	Val	
40		Asp		20			-		25					30		Gly	
40		Ala	35				Ser	40				Gln	45			Gln	
45	Arg 65	50 Thr	Leu	Arg	Glu	Ile 70	55 Lys	Ile	Leu	Leu	Arg 75	60 Phe	Arg	His	Glu	Asn 80	
		Ile			85					90					95	Met Lys	
50		-		100					105					110		Leu	
	Tyr	Gln 130			Arg	Gly	Leu 135			Ile	His	Ser			val	Leu	
55	His	Arg		Leu	Lys	150	Ser				155	Asn	Thr			Asp 160	

Leu Lys Ile Cys Asp Phe Gly Leu Ala Arg Val Ala Asp Pro Asp His

7

					165					170					175	
	Asp	His	Thr	Gly 180	Phe	Leu	Thr	Glu	Tyr 185	Val	Ala	Thr	Arg	Trp 190	Tyr	Arg
5	Ala	Pro	Glu 195	Ile	Met	Leu	Asn	Ser 200	Lys	Gly	Tyr	Thr	Lys 205	Ser	Ile	Asp
	Ile	Trp 210	Ser	Val	Gly	CAa	Ile 215	Leu	Ala	Glu	Met	Leu 220	Ser	Asn	Arg	Pro
	Ile 225	Phe	Pro	Gly	Lys	His 230	Tyr	Leu	qaA	Gln	Leu 235	Asn	His	Ile	Leu	Gly 240
10		Leu	Gly	Ser	Pro 245	Ser	Gln	Glu		Leu 250	Asn	Сув	Ile	Ile	Asn 255	Leu
	Lys	Ala	Arg	Asn 260	Tyr	Leu	Leu	Ser	Leu 265	Pro	His	Lys	Asn	Lys 270	Val	Pro
15	Trp	Asn	Arg 275	Leu	Phe	Pro	Asn	Ala 280	Asp	Ser	Lys	Ala	Leu 285	Asp	Leu	Leu
	qaA	Lys 290	Met	Leu	Thr	Phe	Asn 295	Pro	His	ГÀЗ	Arg	Ile 300	Glu	Val	Glu	Gln
	Ala 305	Leu	Ala	His	Pro	Tyr 310	Leu	Glu	Gln	Tyr	Tyr 315	Asp	Pro	Ser	Asp	Glu 320
20	Pro	Ile	Ala	Glu	Ala 325	Pro	Phe	Lys	Phe	qaA 088	Met	Glu	Leu	Asp	Asp 335	Leu
	Pro	Lys	Glu	<b>Lys</b> 340	Leu	Lys	Glu	Leu	Ile 345	Phe	Glu	Glu	Thr	Ala 350	Arg	Phe
25	Gln	Pro	Gly 355	Tyr	Arg	Ser	Met	360 260	Pro	Pro	Val	Ala	Thr 365	Met	Val	Ser
	-	370			Leu		375	_				380				
	385	-	_		Asn	390		-			395		_			400
30					Tyr 405					410					415	
	_	_		420	Val		_		425					430		
35	_		435	-	Phe		_	440		_			445			
		450			Ala		455					460				
	465			-	_	470		-			475					Phe 480
40		_	-		Leu 485					490		=	-		495	
	_		_	500				_	505	_				510		Asn
45	-		515					520					525			Lys
		530					535					540				Leu
ΕO	545	-		-		550					555		_			Leu 560
50			_		565	_				570					575	Asp Ala
				580					585					590		
55	พาต	. Оту	595		سا جائد	. <b>.</b>		600					-			

			(2)	INE	ORMA	TION	FOF	SEC	] ID	NO:6	:0:			•		
5		<b>(</b> ;)	(B) (C)	QUEN LENG TYPE STRA TOPO	ETH: E: nu ANDEI	2511 nclei NESS	. bas .c ac S: si	e pa id ngle	irs							
10		• -	ii) N ix) F			TYPE	E: cI	AA								
15		(2	(B)	NAM LOC OTI	EATIC	N: 1	L2 RMATI	508 ON:	•		NO : 6	50:				
20			CTG Leu												48	
05			GGC Gly											GAA Glu	96	
25		Leu	AAG Lys 35												144	
30			AGA Arg												192	
35			TTC Phe												240	
40			TTC Phe											_	288	
			GGA Gly												336	
45	AAG	TCC	CCT	GTT	TTC							GAC			384	

Lys Ser Pro Val Phe Ile Ala Gln Val Gly Gln Asp Leu Val Ser Gln

ACG GAG GAG AAG CTC CTA CAG AAG CCG TGC AAA GAA CTC TTT TCT GCC

Thr Glu Glu Lys Leu Gln Lys Pro Cys Lys Glu Leu Phe Ser Ala

TGT GCA CAG TCT GTC CAC GAG TAC CTG AGG GGA GAA CCA TTC CAC GAA Cys Ala Gln Ser Val His Glu Tyr Leu Arg Gly Glu Pro Phe His Glu

_			AGC Ser											528
5			CCG Pro 180											576
10			GGC Gly											624
15		Met	TAT Tyr											672
20			GAG Glu											720
25	 		CAG Gln											768
23			TGC Cys 260											816
30			TAC Tyr											864
35			GCG Ala											912
40			GTC Val											960
AE.			CAC His											1008
45				Leu				Val				Tyr	ATG Met	1056
50			Val				Arg				Pro		TAC Tyr	1104
55		Leu				Туг				ı Gly			CCG Pro	1152

5		CGT Arg											1200
-		ACG Thr	_	 _		Ser	_						1248
10		TGC Cys 420											1296
15		GAG Glu											1344
20		AAC Asn				_		_				_	1392
25	_	GAC Asp		_	_								1440
٠		TCC Ser								_			1488
30		TCC Ser 500							_			CAA Gln	1536
35 ·		ATA Ile											1584
40		ACC Thr										_	1632
45		TAB											1680
		AAG Lys											1728
50		AAC Asn 580	His				Ser				Arg		1776
55		Ala				. TAs				Phe		GGG	1824

5		CCC Pro											1872
		GTG Val											1920
10		AAG Lys											1968
15		GTG Val											2016
20		CAC His 675											2064
25		GTC Val											2112
		CGC Arg											2160
30		CTG Leu							_	_			2208
35	-	CTG Leu											2256
40		CAG Gln 755										AAC Asn	2304
45		Asp				Leu						ACC Thr	2352
	Ile				Val				Asn			AGC Ser 800	2400
50				Ser				Glu				ATG Met	2448
55			Phe				Gly				Met	GAC Asp	2496

131

GAG CTG TAC AAG TAA Glu Leu Tyr Lys 835 2511

5

10

## (2) INFORMATION FOR SEQ ID NO:61:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 836 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- 15 (ii) MOLECULE TYPE: protein
  - (v) FRAGMENT TYPE: internal

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

20	1				Asn 5					10					15	_
	Glu	GJA	Gly	Gly 20	Gly	Lys	Arg	Lys	Gly 25	Lys	Ser	Lys	Lys	Trp 30	Lys	Glu
25	Ile	Leu	Lys 35	Phe	Pro	His	Ile	Ser 40	Gln	Cys	Glu	Asp	Leu 45	Arg	Arg	Thr
	Ile	Asp 50	Arg	Asp	Tyr	Сув	Ser 55	Leu	Сув	Asp	Lys	Gln 60	Pro	Ile	Gly	Arg
	Leu 65	Leu	Phe	Arg	Gln	Phe 70	Сув	Glu	Thr	Arg	Pro 75	Gly	Leu	Glu	Cys	Tyr 80
30	Ile	Gln	Phe	Leu	Asp 85	Ser	Val	Ala	Glu	Tyr 90	Glu	Val	Thr	Pro	Asp 95	Glu
	Lys	Leu	Gly	Glu 100	Lys	Gly	Lys	Glu	Ile 105	Met	Thr	Lys	Tyr	Leu 110	Thr	Pro
35	Lys	Ser	Pro 115	Val	Phe	Ile	Ala	Gln 120	Val	Gly	Gln	Asp	Leu 125	Val	Ser	Gln
	Thr	Glu 130	Glu	Lys	Leu	Leu	Gln 135	Lys	Pro	Cys	Lys	Glu 140	Leu	Phe	Ser	Ala
	Cys 145	Ala	Gln	Ser	Val	His 150	Glu	Tyr	Leu	Arg	Gly 155	Glu	Pro	Phe	His	Glu 160
40	Tyr	Leu	Asp	Ser	Met 165	Phe	Phe	Asp	Arg	Phe 170	Leu	Gln	Trp	Lys	Trp 175	Leu
	Glu	Arg	Gln	Pro 180	Val	Thr	Lys	Asn	Thr 185	Phe	Arg	Gln	Tyr	Arg 190	Val	Leu
45	Gly	Lys	Gly 195	Gly	Phe	Gly	Glu	Val 200	Cys	Ala	Сув	Gln	Val 205	Arg	Ala	Thr
	Gly	Lys 210	Met	Tyr	Ala	Сув	Lys 215	Arg	Leu	Glu	Lys	Lys 220	Arg	Ile	Lys	Lys
	Arg 225	Lys	Gly	Glu	Ser	Met 230	Ala	Leu	Asn	Glu	Lys 235	Gln	Ile	Leu	Glu	Lys 240
50	Val	neA	Ser	Gln	Phe 245	Val	Val	Asn	Leu	Ala 250	Tyr	Ala	Tyr	Glu	Thr 255	Lys
	Asp	Ala	Leu	Сув 260	Leu	Val	Leu	Thr	Ile 265	Met	Asn	Gly	Gly	Asp 270	Leu	ГÀЗ
55	Phe	His	Ile 275	Tyr	Asn	Met	Gly	Asn 280	Pro	Gly	Phe	Glu	Glu 285	Glu	Arg	Ala
	Leu	Phe	Tyr	Ala	Ala	Glu	Ile	Leu	Cys	Gly	Leu	Glu	Asp	Leu	His	Arg

		290					205					200				
	Glu		Thr	17a 1	There	7 ~~	295	Len	Tard	Dro	<i>(</i> 111)	300	Tla	T 011	T 011	7 ~~
	305					310					315					320
5	Asp	Tyr	Gly	His	Ile 325	Arg	Ile	Ser	Asp	Leu 330	Gly	Leu	Ala	Val	Lys 335	Ile
	Pro	Glu	Gly	Asp 340	Leu	Ile	Arg	Gly	Arg 345	Val	Gly	Thr	Val	Gly 350	Tyr	Met
	Ala	Pro	Glu 355	Val	Leu	Asn	Asn	Gln 360	Arg	Tyr	Gly	Leu	Ser 365	Pro	Asp	Туг
10	Trp	Gly 370	Leu	Gly	Сув	Leu	Ile 375	Tyr	Glu	Met	Ile	Glu 380		Gln	Ser	Pro
	Phe 385		Gly	Arg	Lys	Glu 390		Val	Lys	Arg	Glu 395		Val	ĄsĄ	Arg	Arg
15		Leu	Glu	Thr	Glu 405		Val	Tyr	Ser	His 410		Phe	Ser	Glu	Glu 415	
,0	ГÀЗ	Ser	Ile	Cys 420		Met	Leu	Leu	Thr 425		Asp	Ala	Lys	Gln 430	. ——	Leu
	Gly	Сув	Gln 435		Glu	Gly	Ala	Ala 440		Val	Lys	Arg	His 445		Phe	Phe
20	Arg	Asn 450	Met	Asn	Phe	Lys	Arg 455		Glu	Ala	Gly	Met		Asp	Pro	Pro
	Phe 465		Pro	Asp	Pro	Arg		Val	Tyr	Сув	Lys 475		Val	Leu	Asp	Ile
25		Gln	Phe	Ser	Thr 485		Lys	Gly	Val	Asn 490		Asp	His	Thr	Asp 495	-
20	Asp	Phe	Tyr	Ser 500		Phe	Ser	Thr	Gly 505		Val	Ser	Ile	Pro 510		Glr
	Asn	Glu	Met 515		Glu	Thr	Glu	Cys 520		Lys	Glu	Leu	Asn 525		Phe	Gly
30	Pro	Asn 530	Gly	Thr	Leu	Pro	Pro 535		Leu	Asn	Arg	Asn 540		Pro	Pro	Glu
	Pro 545		Lys	Lys	Gly	Leu 550		Gln	Arg	Leu	Phe 555		Arg	Gln	His	Glr 560
35		Asn	Ser	Lys	Ser 565		Pro	Ser	Ser	Lys 570		Ser	Phe	Asn	His 575	
	Ile	Asn	Ser	Asn 580		Val	Ser	Ser	Asn 585		Thr	Gly	Ser	Ser 590		Asr
	Pro	Pro	Val 595		Thr	Met	Val	Ser 600		Gly	Glu	Glu	Leu 605		Thr	Gl
40	Val	Val 610	Pro	Ile	Leu	Val	Glu 615		Asp	Gly	Asp	Val 620		Gly	His	Lys
·	Phe 625		Val	Ser	Gly	Glu 630		Glu	Gly	Asp	Ala 635		Tyr	Gly	Lys	Let 640
45		Leu	Lys	Phe	Ile 645		Thr	Thr	Gly	Lys 650		Pro	Val	Pro	Trp 655	
,-	Thr	Leu	Val	Thr 660		Leu	Thr	Tyr	Gly 665		Gln	Cys	Phe	Ser 670		Туз
	Pro	Asp	His 675		Lys	Gln	His	Asp 680		Phe	Lys	Ser	Ala 685		Pro	Glı
50	Gly	Tyr 690	Val	Gln	Glu	Arg	Thr 695		Phe	Phe	Lys	Asp		Gly	Asn	Ту
	Lys 705	Thr	Arg	Ala	Glu	Val 710		Phe	Glu	Gly	Asp 715		Leu	Val	Asn	Arg
55			Leu	Lys	Gly 725		Asp	Phe	Lys	Glu 730		Gly	Asn	Ile	Leu 735	Gl
	His	Lvs	Leu	Glu		Asn	Tvr	Asn	Ser		Asn	Val	Tyr	Ile		

. 133

				740					745					750			
	Asp	Lys	Gln 755	Lys	Asn	Gly	Ile	Lys 760	Val	Asn	Phe	Lys	Ile 765	Arg	His	Asn	
5	Ile	Glu 770	Asp	Gly	Ser	Val	Gln 775	Leu	Ala	Asp	His	Tyr 780	Gln	Gln	Asn	Thr	
	Pro 785	Ile	Gly	Asp	Gly	Pro 790	Val	Leu	Leu	Pro	Asp 795	Asn	His	Tyr	Leu	Ser 800	
	Thr	Gln	Ser	Ala	Leu 805	Ser	ГÀЗ	Asp	Pro	Asn 810	Glu	Lys	Arg	qaA	His 815	Met	
10	Val	Leu	Leu	Glu 820	Phe	Val	Thr	Ala	Ala 825	Gly	Ile	Thr	Leu	Gly 830	Met	qsA	
	Glu	Leu	Tyr 835	Lys													
15			(2)	INE	ORM	ATION	FOF	SEÇ	) ID	NO:6	52:						
		( j				CHARA 1893											
20						iclei DNESS			2								
						(: li											
			- 1	OLEC		TYPE	: cI	ONA									
25					-	EY: C		_	equer	ıce							
						ON: 1 INFOR											
30		()	ci) S	EQUE	ENCE	DESC	RIPT	: NOI	SEC	) ID	NO:	52:					
						CGT Arg											48
35	1		3		5	3				10	-1-				15	,	
						GTC Val											96
	-			20				•	25	•	•			30			
40						GGA Gly											144
	_		_			-			-			-	-			•	
45						ATC											192
45	Glu	Arg 50	Asn	vai	Ala	Ile	ьув 55	гуs	Leu	ser	Arg	Pro 60	Phe	Gin	Asn	Gin	
						GCC											240
50	fnr 65	HIS	Ala	гуу	Arg	Ala 70	Tyr	Arg	GIU	Leu	75	Leu	Met	гÀв	Cys	80	
						ATT											288
55	ABN	H18	пЛв	asn	85	Ile	σтλ	ьeu	neu	Asn 90	vaı	rne	rnr	510	G1n 95	тÀв	
JJ	TCC	CTA	GAA	GAA	TTT	CAA	GAT	GTT	TAC	ATA	GTC	ATG	GAG	CTC	ATG	GAT	336

•										134							•	
	Ser	Leu	Glu	Glu 100	Phe	Gln	Asp	Val	Tyr 105	Ile	Val	Met	Glu	Leu 110	Met	Asp		
	GCA	AAT	СТТ	TGC	CAA	GTG	ATT	CAG	ATG	GAG	СТА	CAT	СУТ	AAD	ADA	ΔͲŒ	384	
5		Asn															501	
	TCC	TAC	CTT	CTC	TAT	CAG	ATG	CTG	TGT	GGA	ATC	DAA	CAC	CTT	САТ	TCT	432	
		Tyr															102	
10		130					135			_		140						
		GGA															480	
		Gly	lle	TTE	His		Asp	Leu	Lys	Pro		Asn	Ile	Val	Val			
15	145					150					155					160		
10	тст	GAT	TGC	АСТ	тта	DAG	ΔΤΤ	ىئىلىك	GAC	רוייניי	CCT	СТС	GCC	AGG	ארייזי	CCA	528	
		Asp								*							320	
					165	-1-				170	,				175			
20	GGA	ACG	AGT	TTT	ATG	ATG	ACG	CCT	TAT	GTA	GTG	ACT	CGC	TAC	TAC	AGA	576	
	Gly	Thr	Ser	Phe	Met	Met	Thr	Pro	Tyr	Val	Val	Thr	Arg	Tyr	Tyr	Arg		
				180					185					190				
		CCC															624	
25	Ala	Pro	Glu 195	Val	Ile	Leu	Gly	Met 200	Gly	Tyr	Lys	Glu	Asn 205	Val	Asp	Leu		
-	TGG	TCT	GTG	GGG	TGC	ATT	ATG	GGA	GAA	ATG	GTT	TGC	CAC	AAA	ATC	CTC	672	
		Ser																
30	_	210		-	-		215	-				220		-				
	TTT	CCA	GGA	AGG	GAC	TAT	ATT	GAT	CAG	TGG	AAT	AAA	GTT	ATT	GAA	CAG	720	
		Pro	Gly	Arg	qaA	Tyr	Ile	Авр	Gln	Trp	Asn	Lys	Val	Ile	Glu	Gln		
0.5	225					230					235					240		
35		~~~		~~~														
		GGA															768	
	Deu	Gly	1111	PLO	245	PIO	Giu	Pne	Mec	250	ьув	Leu	GIII	PIO	255	Val		
40	AGG	ACT	TAC	GTT	GAA	AAC	AGA	CCT	AAA	TAT	GCT	GGA	TAT	AGC	TTT	GAG	816	
	Arg	Thr	Tyr	Val	Glu	Asn	Arg	Pro	Lys	Tyr	Ala	Gly	Tyr	Ser	Phe	Glu		
				260					265					270				
45		CTC															864	
40	гув	Leu	275	Pro	Asp	vaı	Leu		Pro	ATA	Asp	ser		HIS	Asn	гла		
			215					280					285					
	CTT	AAA	GCC	AGT	CAG	GCA	AGG	GAT	TTG	тта	TCC	AAA	ATG	CTG	GTA	ATA	912	
		Lys																
50		290					295	-				300						
		GCA															960	
		Ala	Ser	ГÀа	Arg		Ser	Val	Asp	Glu			Gln	His	Pro	-		
55	305					310				•	315					320		
JJ	איני	ייממ	מיירי	ጥርር	ጥልጥ	ርንጥ		יחרותי	(ZN N	GC3	GV v	CCm	ር ር	ררא	CCR	AAG	1008	
	424 G	W	GIÇ	100	TAL	GMI	CCI	101	GAA	GUA	GMA	GÇI	CCA	CCA	CCM	HAG		
																		1

										133							•
	Ile	Asn	Val	Trp	Tyr 325	Asp	Pro	Ser	Glu	Ala 330	Glu	Ala	Pro	Pro	Pro 335	Lys	
	ΔТС	CCT	GAC	ממ	CAG	מידיני	СУТ	CAD	ACC	CAA	ראכ	מים	מידמ	CAA	GNG	ጥርር	1056
5					Gln												1030
	AAA	GAA	TTG	ATA	TAT	AAG	GAA	GTT	ATG	GAC	TTG	GAG	GAG	AGA	ACC	AAG	1104
					Tyr												
10			355					360					365			-	
					CGG												1152
	Asn	-	Val	Ile	Arg	GTA		Pro	Ser	Pro	Leu		Gln	Val	Gln	Gln	
15		370					375					380					
10	TGG	GAT	CCA	CCG	GTC	GCC	ACC	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	1200
					Val												
	385	-				390					395	-				400	
20					CCC												1248
	Thr	GIŸ	vaı	vaı	Pro 405	TIE	ьeu	vaı	GIU		Asp	GLY	АБР	vai	ASN 415	GIÀ	
					403					410					413		
	CAC	AAG	TTC	AGC	GTG	TCC	GGC	GAG	GGC	GAG	GGC	ĠAT	GCC	ACC	TAC	GGC	1296
25					Val												
		_		420			_		425		_	_		430	_	_	
					AAG												1344
30	гуя	nen	435	ren	Lys	Pile	TIE	440	THE	Thr	GIY	тАв	445	PIO	vai	PIO	
50								140					110				
	TGG	CCC	ACC	CTC	GTG	ACC	ACC	CTG	ACC	TAC	GGC	GTG	CAG	TGC	TTC	AGC	1392
	Trp	Pro	Thr	Leu	Val	Thr	Thr	Leu	Thr	Tyr	Gly	Val	Gln	СЛа	Phe	Ser	
O.E.		450					455					460					
35	ccc	mr c	000	~~~	C) C	איזייר	7 7 C	CNC	a a	<b>a</b>	man ca	mmc	220	maa.	ccc	חייות	1440
					CAC His												1440
	465	-1-	110	wob	1110	470	۵,5	0111	MIS	rob	475	rnc	טעט	-	712U	480	
40					GTC												1488
	Pro	Glu	Gly	Tyr	Val	Gln	Glu	Arg	Thr		Phe	Phe	ГÄâ	Asp		Gly	
					485					490					495		
	מממ	тас	PVC	ልሮሮ	CGC	פכר	GAG	GTG	ממ	יייייי	GAG	GGC	GAC	ACC	CTG	GTG	1536
45					Arg												1330
		-7-	_,.	500	5				505	1110		·		510			
					CTG												1584
	Asn	Arg		Glu	Leu	Lys	Gly		Asp	Phe	Lys	Glu	_	Gly	Asn	Ile	
50			515					520					525				
	ריודים	GGG	ראר	עעמ	CTG	GAG	ጥልሮ	ልልሮ	יי. איז רי	<u>አ</u> አሮ	אפר	CAC	אאר	GTC	ጥልጥ	ATC	1632
					Leu												
		530					535		- <u>,</u> -			540			4	-	
55														•			
	ATG	GCC	GAC	AAG	CAG	AAG	AAC	GGC	ATC	AAG	GTG	AAC	TTC	AAG	ATC	CGC	1680
																	•

										136		_					
	Met 545	Ala	Asp	Lys	Gln	Lys 550	Asn	Gly	Ile	Lys	Val 555	Asn	Phe	Lys	Ile	Arg 560	
5									CAG Gln								1728
10									GTG Val 585								1776
15									AAA Lys								1824
15									ACC Thr								1872
20		GAC Asp					TAA										1893
25			(2)	INI	FORM	ATION	I FOI	R SE	O ID	NO: 6	53:						
30			(A) (B) (C) (D)	LENC TYPI STRI	STH: E: ar ANDEI OLOGY	CHARA 630 mino ONESS Y: li	amin acid 3: si inean	no ao i ingle	cids								
35		(7	7) FI	RAGMI	ENT 7	TYPI : TYPE	int	erna		3 TD		ea .	,				
										-							
	1		•		5		-		Asn	10	•				15	-	
40				20					Arg 25					30			
			35					40	Сув		•		45				
45	Glu	Arg 50	Asn	Val	Ala	Ile	Lys 55	Lys	Leu	Ser	Arg	Pro 60	Phe	Gln	Asn	Gln	
	Thr 65	His	Ala	Lys	Arg	Ala 70	Tyr	Arg	Glu	Leu	Val 75	Leu	Met	Lys	Сув	Val 80	
	Asn	His	Lys	Asn	Ile 85	Ile	Gly	Leu	Leu	Asn 90	Val	Phe	Thr	Pro	Gln 95	Lys	
50	Ser	Leu	Glu	Glu 100	Phe	Gln	Asp	Val	Tyr 105	Ile	Val	Met	Glu	Leu 110	Met	Asp	
	Ala	Asn	Leu 115	Сув	Gln	Val	Ile	Gln 120	Met	Glu	Leu	Asp	His 125	Glu	Arg	Met	
55	Ser	Tyr 130		Leu	Tyr	Gln	Met 135		Cys	Gly	Ile	Lys 140		Leu	His	Ser	
- <del>-</del>	Ala		Ile	Ile	His	Arg		Leu	Lys	Pro	Ser		Ile	Val	Val	Lys	

	145					150					155					160
		Asp	Cys	Thr	Leu 165		Ile	Leu	Asp	Phe 170		Leu	Ala	Arg	Thr 175	
5		Thr		180					185				_	190	_	_
		Pro	195					200					205		-	
40		Ser 210					215					220		_		
10	225	Pro				230					235					240
		Gly			245					250	-				255	
15		Thr		260					265	_		_	_	270		
	_	Leu	275		_			280			-		285			•
20		290 Ala					295	_				300				
	305	Asn				310					315					320
		Pro			325					330					335	-
25		Glu		340					345					350		_
		Gly	355					360		_			365	_		-
30		370 Asp					375					380				
	385	Gly				390					395					400
		Lys			405					410					415	
35	Lys	Leu	Thr	420 Leu	Lys	Phe	Ile	Cys	425 Thr	Thr	Gly	Lys	Leu	430 Pro	Val	Pro
	Trp	Pro	435 Thr	Leu	Val	Thr	Thr	440 Leu	Thr	Tyr	Gly	Val	445 Gln	Сув	Phe	Ser
40		450 Tyr	Pro	Asp	His		455 Lys	Gln	His	Asp	Phe	460 Phe	Lys	Ser	Ala	Met
	465 Pro	Glu	Gly	Tyr		470 Gln	Glu	Arg	Thr		475 Phe	Phe	Lys			480 Gly
45	Asn	Tyr	Lys		485 Arg	Ala	Glu	Val	_	490 Phe	Glu	Gly	Asp	Thr	495 Leu	Val
40	Asn	Arg		500 Glu	Leu	Ьув	Gly		505 Asp	Phe	Lys	Glu	_	510 Gly	Asn	Ile
	Leu	Gly 530	515 His	Lys	Leu	Glu	Tyr 535	520 Asn	Tyr	Asn	Ser	His 540	525 Asn	Val	Tyr	Ile
50	Met 545	Ala	Asp	Lys	Gln	Lys 550		Gly	Ile	Lys	Val 555		Phe	Гув	Ile	
		Asn	Ile	Glu	Asp 565		Ser	Val	Gln	Leu 570		Asp	His	Tyr	Gln 575	560 Gln
55	Asn	Thr	Pro	Ile 580		Asp	Gly	Pro	Val 585		Leu	Pro	Asp	Asn 590		туг
	Leu	Ser	Thr		Ser	Ala	Leu	Ser		Asp	Pro	Asn	Glu		Arg	Asp

138

595 600 605 His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly 615 Met Asp Glu Leu Tyr Lys 5 (2) INFORMATION FOR SEQ ID NO:64: (i) SEQUENCE CHARACTERISTICS: 10 (A) LENGTH: 1821 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA 15 (ix) FEATURE: (A) NAME/KEY: Coding Sequence (B) LOCATION: 1...1818 20 (D) OTHER INFORMATION: (xi) SEQUENCE DESCRIPTION: SEQ ID NO:64: ATG TCT CAG GAG AGG CCC ACG TTC TAC CGG CAG GAG CTG AAC AAG ACA 48 Met Ser Gln Glu Arg Pro Thr Phe Tyr Arg Gln Glu Leu Asn Lys Thr 25 ATC TGG GAG GTG CCC GAG CGT TAC CAG AAC CTG TCT CCA GTG GGC TCT Ile Trp Glu Val Pro Glu Arg Tyr Gln Asn Leu Ser Pro Val Gly Ser 30 20 GGC GCC TAT GGC TCT GTG TGT GCT GCT TTT GAC ACA AAA ACG GGG TTA Gly Ala Tyr Gly Ser Val Cys Ala Ala Phe Asp Thr Lys Thr Gly Leu 35 35 CGT GTG GCA GTG AAG AAG CTC TCC AGA CCA TTT CAG TCC ATC ATT CAT 192 Arg Val Ala Val Lys Lys Leu Ser Arg Pro Phe Gln Ser Ile Ile His 50 40 GCG AAA AGA ACC TAC AGA GAA CTG CGG TTA CTT AAA CAT ATG AAA CAT 240 Ala Lys Arg Thr Tyr Arg Glu Leu Arg Leu Leu Lys His Met Lys His GAA AAT GTG ATT GGT CTG TTG GAC GTT TTT ACA CCT GCA AGG TCT CTG 288 Glu Asn Val Ile Gly Leu Leu Asp Val Phe Thr Pro Ala Arg Ser Leu 45 GAG GAA TTC AAT GAT GTG TAT CTG GTG ACC CAT CTC ATG GGG GCA GAT 336 Glu Glu Phe Asn Asp Val Tyr Leu Val Thr His Leu Met Gly Ala Asp 50 105 CTG AAC AAC ATT GTG AAA TGT CAG AAG CTT ACA GAT GAC CAT GTT CAG 384 Leu Asn Asn Ile Val Lys Cys Gln Lys Leu Thr Asp Asp His Val Gln 120 55 TTC CTT ATC TAC CAA ATT CTC CGA GGT CTA AAG TAT ATA CAT TCA GCT 138

										139							
	Phe	Leu 130	Ile	Tyr	Gln	Ile	Leu 135	Arg	Gly	Leu	Lys	Tyr 140	Ile	His	Ser	Ala	
5		ATA Ile															480
10		Cys															528
15		GAA Glu														_	576
		ATG Met															624
20		GGA Gly 210															672
25		ACA Thr															720
30		CCA Pro															768
35		TAT Tyr									•						816
		TTT Phe															864
40	_	GTA Val 290															912
45	_	GCC Ala															960
50		CCT Pro															1008
55		AAA Lys															1056
	CTT	GAC	CAA	gaa	GAG	ATG	GAG	TCC	GAG	GAT	CCA	CCG	GTC	GCC	ACC	ATG	1104

	Leu	Asp	Gln	Glu	Glu	Met	Glu	Ser	Glu	Asp	Pro	Pro	Val	Ala	Thr	Met	
		•	355					360					365				
5			AAG Lys														1152
		370	•	•	•		375			1		380					
			GAC														1200
10	385	ьeu	Asp	GTÀ	цан	390	ASII	GTÀ	HIS	гАа	395	ser	vaı	ser	GIA	400	
			GGC														1248
	Gly	Glu	Gly	Asp	Ala 405	Thr	Tyr	Gly	Lys	Leu 410	Thr	Leu	Lys	Phe	Ile 415	Cys	
15			GGC														1296
	Thr	Thr	Gly	Lys 420	Leu	Pro	Val	Pro	Trp 425	Pro	Thr	Leu	Val	Thr 430	Thr	Leu	
20	ACC	TAC	GGC	GTG	CAG	TGC	TTC	AGC	CGC	TAC	ccc	GAC	CAC	ATG	DAG	CAG	1344
			Gly 435								-						
	CN C	C2 C	TTC	THE CO	7 7 C	maa.	cca		000	<b>G3.3</b>	000	m		a. a	a. a	000	1200
25		Asp	Phe				Ala					Tyr					1392
		450					455					460					
	Thr		TTC Phe														1440
30	465					470					475					480	
			GAG Glu														1488
35					485				•	490				-	495		
			AAG Lys														1536
•			•	500		4			505	<b></b> 1		_,_		510	-1-		
40			AGC Ser														1584
	-7.	non.	515		A.J.I.	VA.	-7-	520	Mec	ALG	мър	Був	525	цув	ABII	GIY	•
AE .			GTG														1632
45	TTE	ьув 530	Val	Asn	Pne	гув	535	Arg	HIS	Asn	TTE	540	Asp	GIÀ	ser	vai	
			GCC														1680
50	Gln 545	Leu	Ala	Asp	His	Tyr 550	Gln	Gln	Asn	Thr	Pro 555	Ile	Gly	Asp	Gly	Pro 560	
	GTG	CTG	CTG	CCC	GAC	AAC	CAC	TAC	CTG	AGC	ACC	CAG	TCC	GCC	CTG	AGC	1728
			Leu														
55	ААА	GAC	CCC	AAC		AAG	CGC	ФĀТ	CAC		GTC	CTG	Сла	GAG		GTG	1776
	<b>-</b> •							~~~				-20					

141

										1741							
	Lys	ĄaĄ	Pro	Asn 580	Glu	Lys	Arg	Asp	His 585	Met	Val	Leu	Leu	Glu 590	Phe	Val	
5		GCC Ala													TAA		1821
4.0			(2)	) IN	FORM	ATIO	v Foi	R SEG	Q ID	NO:	55:						
10		(:	(A) (B)	EQUE LENC TYP) STR	GTH: E: ar	606 mino	amin acid	no ao 1	cids								
15			(D)	TOP	OLOG:	Y: 1:	inea	r		-							
				MOLE( RAGMI													
20				EQUI													
	1	Ser			5					10					15		
25		Trp		20			_	_	25					30	•		
		Ala	35					40					45		_		
20		Val					55					60					
30	65	Lys				70					75				-	80	
		Asn			85					90				_	95		
35		Glu		100					105					110		-	
		Asn	115					120					125				
40		Leu 130					135					140					
70	145	Ile	TIE		Arg								Ата	vaı	ASD	160	
		Сув	Glu										Arg	His	Thr 175	Asp	
45	Asp	Glu	Met	Thr 180		Tyr	Val	Ala	Thr 185	Arg	Trp	Tyr	Arg	Ala 190		Glu	
	Ile	Met	Leu 195		Trp	Met	His	Tyr 200			Thr	Val	Asp 205		Trp	Ser	
	Val	Gly 210		Ile	Met	Ala	Glu 215		Leu	Thr	Gly	Arg 220		Leu	Phe	Pro	
50	Gly	Thr	Asp	His	Ile	Авр		Leu	Lys	Leu	Ile		Arg	Leu	Val	Gly	
	225					230					235					240	
		Pro			245					250					255		
55	Asn	Tyr	Ile	Gln 260	Ser	Leu	Thr	Gln	Met 265	Pro	Lys	Met	Asn	Phe 270	Ala	Asn	
	Val	Phe	Ile	Gly	Ala	Asn	Pro	Leu	Ala	Val	Asp	Leu	Leu	Glu	ГÀа	Met	

142

			275					280					285			
	Leu	Val 290	Leu	Asp	Ser	Asp	Lys 295	Arg	Ile	Thr	Ala	Ala 300	Gln	Ala	Leu	Ala
5	His 305	Ala	Tyr	Phe	Ala	Gln 310	Tyr	His	Asp	Pro	Авр 315	Asp	Glu	Pro	Val	Ala 320
	qaA	Pro	Tyr	Ąsp	Gln 325	Ser	Phe	Glu	Ser	Arg 330	Asp	Leu	Leu	Ile	Asp 335	Glu
	Trp	Lys	Ser	Leu 340	Thr	Tyr	qeA	Glu	Val 345	Ile	Ser	Phe	Val	Pro 350	Pro	Pro
10	Leu	Asp	Gln 355	Glu	Glu	Met	Glu	Ser 360	Glu	Asp	Pro	Pro	Val 365	Ala	Thr	Met
	Val	Ser 370	ГÀЗ	Gly	Glu	Glu	Leu 375	Phe	Thr	Gly	Val	Val 380	Pro	Ile	Leu	Val
15	Glu 385	Leu	Asp	Gly	ĄsĄ	Val 390	Asn	Gly	His	Lys	Phe 395	Ser	Val	Ser	Gly	Glu 400
		Glu			405					410					415	
	Thr	Thr	Gly	Lys 420	Leu	Pro	Val	Pro	Trp 425	Pro	Thr	Leu	Val	Thr 430	Thr	Leu
20	Thr	Tyr	Gly 435	Val	Gln	Cys	Phe	Ser 440	Arg	Tyr	Pro	Asp	His 445	Met	Lys	Gln
		Asp 450			-		455				_	460				_
25	Thr 465	Ile	Phe	Phe	ràs	Asp 470	Asp	Gly	Asn	Tyr	Lys 475	Thr	Arg	Ala	Glu	Val 480
	Lys	Phe	Glu	Gly	Asp 485	Thr	Leu	Val	Asn	Arg 490	Ile	Glu	Leu	ГÀв	Gly 495	
	Asp	Phe	Lys	Glu 500	Asp	Gly	Asn	Ile	Leu 505	Gly	His	Lys	Leu	Glu 510	Tyr	Asn
30	Tyr	Asn	Ser 515	His	Asn	Val	Tyr	Ile 520	Met	Ala	Asp	Lys	Gln 525	Lys	Asn	Gly
		Lys 530					535					540				
35	545	Leu				550					555					560
		Leu			565					570					575	
		Asp		580					585					590	Phe	Val
40	Thr	Ala	Ala 595	Gly	Ile	Thr	Leu	Gly 600	Met	Asp	Glu	Leu	Tyr 605	Lys		
			(2)	IN	PORM	ATIO	N FOI	R SE(	Q ID	NO:	56:					
45		(:	(B) (C)	LENC TYPI STR	TH: E: n ANDEI	291: icle: ONES:	ACTEI 3 bas ic ac 5: s:	se pa cid ingle	airs							
50			ii) ! ix) !	OLE	CULE					*						

142

(A) NAME/KEY: Coding Sequence (B) LOCATION: 1...2910

(D) OTHER INFORMATION:

143

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

5				GAG Glu													48
10				GAA Glu 20													96
15				TCC Ser													144
				GAA Glu													192
20				GAC Asp													240
25				CCT Pro													288
30				GGT Gly 100													336
35	Leu	Thr	Leu 115	CCG Pro	Asp	Leu	Ala	Glu 120	Gln	Phe	Ala	Pro	Pro 125	qaA	Ile	Ala	384
				CTT Leu													432
40				ACT Thr													480
45				CTT Leu													528
50				CAC His 180													576
55				CCT Pro													624
	TTA	GCT	CCA	GAA	GTA	CAA	AGC	TCC	GAA	GAA	TAT	ATT	CAG	CTA	TTG	AAG	672

										1 77							
	Leu	Ala 210	Pro	Glu	Val	Gln	Ser 215	Ser	Glu	Glu	Tyr	Ile 220	Gln	Leu	Leu	Lys	
5	AAG Lys 225	CTT Leu	ATT Ile	AGG Arg	TCG Ser	CCT Pro 230	AGC Ser	ATA Ile	CCT Pro	CAT His	CAG Gln 235	TAT Tyr	TGG Trp	CTT Leu	ACG Thr	CTT Leu 240	720
10			TTG Leu														768
			TTG Leu														816
15			TTC Phe 275														864
20			GAA Glu					ACT					CGA				912
25			CTG Leu									ACT					960
30			AAT Asn														1008
			TCG Ser														1056
35			TTT Phe 355														1104
40			ACA Thr														1152
45			GAT Asp														1200
50			GAA Glu														1248
			AAA Lys														1296
55	CAG	GAT	CAA	GTT	GTC	AAA	GAA	GAT	AAT	ATT	GAA	GCT	GTA	GGG	AAA	AAA	1344

										145							
	Gln	Asp	Gln 435	Val	Val	Lys	Glu	Asp 440	Asn	Ile	Glu	Ala	Val 445	Gly	Lys	Lys	
	TTA	CAT	GAA	TAT	AAC	ACT	CAG	TTT	CAA	GAA	AAA	AGT	CGA	GAA	TAT	GAT	1392
5	Leu	His 450	Glu	Tyr	Asn	Thr	Gln 455	Phe	Gln	Glu	Lys	Ser 460	Arg	Glu	Tyr	Asp	
	AGA	TTA	TAT	GAA	GAA	TAT	ACC	CGC	ACA	TCC	CAG	GAA	ATC	ĊAA	ATG	AAA	1440
10	Arg 465	Leu	Tyr	Glu	Glu	Tyr 470	Thr	Arg	Thr	Ser	Gln 475	Glu	Ile	Gln	Met	Lys 480	
						GCA											1488
	Arg	Thr	Ala	Ile	Glu 485	Ala	Phe	Asn	Glu	Thr 490	Ile	ГÀЗ	Ile	Phe	Glu 495	Glu	
15																	
						GAG											1536
	Gin	Сув	GIN	500	GIN	Glu	Arg	Tyr	505	гуя	Glu	Tyr	Ile	Glu 510	ГЛа	Phe	
20	AAA	CGT	GAA	GGC	AAT	GAG	AAA	GAA	ATA	CAA	AGG	ATT	ATG	CAT	AAT	TAT	1584
	пув	Arg	515	GIY	Asn	Glu	гÀа	520	Ile	GIn	Arg	Ile	Met 525	His	Asn	Tyr	
25						CGA											1632
23	мвр	530	nea	пув	ser	Arg	535	ser	GIU	Tie	Ile	Asp 540	ser	Arg	Arg	Arg	
						AAG											1680
30	545	GIU	GIU	Asp	ьеи	Lys 550	гÀг	GIN	Ala	Ala	G1u 555	Tyr	Arg	Glu	Ile	Asp 560	
						ATT											1728
	пув	Arg	Mec	Asn	565	Ile	гув	Pro	Asp	Leu 570	Ile	Gln	Leu	Arg	Lys 575	Thr	
35																	
	AGA	GAC	CAA	TAC	TTG	ATG	TGG	TTG	ACT	CAA	AAA	GGT	GTT	CGG	CAA	AAG	1776
				580		Met			585					590			
40	AAG	TTG	AAC	GAG	TGG	TTG	GGC	AAT	GAA	AAC	ACT	GAA	GAC	CAA	TAT	TCA	1824
			595			Leu		600					605				
45	CTG	GTG	GAA	GAT	GAT	GAA	GAT	TTG	CCC	CAT	CAT	GAT	GAG	AAG	ACA	TGG	1872
40		610				Glu	615					620					
						AAC											1920
50	ASN 625	val	GTÅ	ser	ser	Asn 630	arg	ASN	гуѕ	Ala	Glu 635	Asn	ren	Leu	Arg	Gly 640	
						•											
						TTT											1968
	nys	wra	ush	GTÅ	645	Phe	пеп	val	arg	650	ser	ser	тув	GIN	655	сув	
55																	
	TAT	GCC	TGC	TCT	GTA	GTG	GTG	GAC	GGC	GAA	GTA	AAG	CAT	TGT	GTC	ATA	2016

										140							
	Tyr	Ala	Cys	Ser 660	Val	Val	Val	Asp	Gly 665	Glu	Val	Lys	His	Cys 670	Val	Ile	
	AAC	AAA	ACA	GCA	ACT	GGC	TAT	GGC	TTT	GCC	GAG	ccc	TAT	AAC	TTG	TAC	2064
5	Asn	Lys	Thr 675	Ala	Thr	Gly	Tyr	Gly 680	Phe	Ala	Glu	Pro	Tyr 685	Asn	Leu	Tyr	
	AGC	TCT	CTG	AAA	GAA	CTG	GTG	CTA	CAT	TAC	CAA	CAC	ACC	TCC	CTT	GTG	2112
				Lys													
10	CAC	690	አክሮ	ana.	שפט	C TO C	695	ama	202		000	700	aa.	am.			07.50
				GAC Asp													2160
	705			тор		710	11511	V (1.1	1111	неи	715	TYT	FLO	Val	TYL	720	
15																, 20	
	CAG	CAG	AGG	CGA	CAG	GAT	CCA	CCG	GTC	GCC	ACC	ATG	GTG	AGC	AAG	GGC	2208
	Gln	Gln	Arg	Arg	Gln	qaA	Pro	Pro	Val	Ala	Thr	Met	Val	Ser	Lys	Gly	
					725					730					735		
20	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	GTC	GAG	CTG	GAC	GGC	2256
	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	Val	Glu	Leu	Asp	Gly	
				740					745					750			
	GAC	CITIN.	አአሮ	GGC	מאמ	מממ	ጥጥር፣	NCC	CTC	maa.	000	030	000	aza	~~~	a m	2204
25				Gly													2304
	F		755	1		-,-		760			O_j		765	0.44	O <sub>2</sub> y	пор	
				GGC													2352
30	Ala		Tyr	Gly	Lys	Leu		Leu	Lys	Phe	Ile	-	Thr	Thr	Gly	Lys	
30		770					775					780					
	CTG	CCC	GTG	CCC	TGG	CCC	ACC	CTC	GTG	ACC	ACC	CTG	ACC	TAC	GGC	GTG	2400
				Pro													
25	785					790					795					800	
35	CNG	maa	መጥር	AGC	ccc	TT'N CT	cca	CZC	ara.	3 000	220	as a	an a	a. a	mmc	mma	2440
	_		_	Ser													2448
		-,-			805	-1-		P	****	810	#y5	QIII	1113	пор	815	FIIC	
40				ATG													2496
	гув	Ser	Ala	Met	Pro	GIu	GIY	Tyr		Gln	Glu	Arg	Thr		Phe	Phe	
				B20					825					830			
	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	GTG	AAG	TTC	GAG	GGC	2544
45				Gly													2022
	_		835				_	840	_				845			-	
				GTG													2592
50	Авр	850	Leu	Val	Asn	Arg	855	GIU	Leu	ràs	GIĀ	860	Asp	Pne	гÀв	GIU	
-		030					çç					000					
	GAC	GGC	AAC	ATC	CTG	GGG	CAC	AAG	CTG	GAG	TAC	AAC	TAC	AAC	AGC	CAC	2640
		Gly	Asn	Ile	Leu		His	Lys	Leu	Glu	Tyr	Asn	Tyr	Asn	Ser	His	
ce	865					870					875					880	
55	מממ	CITIC!	ጥለጥ	חייית	בעדת	aaa	an a	224	C 7 C	***	ת א ת	acc	אייים	አአጣ	ama	מממ	2600
	MMU	GIC	THI	ATC	MIG	GUU	GAC	AAG	CAG	AAG	AAC	GGC	AIC	HAG	GTG	MAC	2688

										147							
	Asn	Val	Tyr	Ile	Met 885	Ala	Asp	Lys	Gln	Lys 890	Asn	Gly	Ile	Lys	Val 895	Asn	
5												GTG Val					2736
10												CCC Pro					2784
45												AGC Ser 940					2832
15												GTG Val					2880
20				GGC Gly							TAA						2913
25			(2)	INI	FORM	ATIO1	1 FOI	R SE(	) ID	NO:	57:		•				· .
30			(A) (B) (C) (D)	EQUEI LENG TYPI STRI TOPG	FTH: E: ar ANDEI OLOGY	970 mino ONESS	amin acio 3: s: inean	no ad i ingle	cids								
35		(1	/) FI	RAGMI SEQUI	ent :	CYPE:	int	cerna	al	Q ID	NO:	57:					
	1				5	-		•	_	10		туг	_	_	15	_	
40				20					25		-	Asp		30			
		_	35					40	_	÷			45			Ala Gly	
45		50					55				_	60 Tyr					
	65 Lys	Ile	Ser	Pro		70 Thr	Pro	Lys	Pro	_	75 Pro	Pro	Arg	Pro	Leu 95	80 Pro	
50	Val	Ala	Pro	Gly 100		Ser	Lys	Thr	Glu 105		Asp	Val	Glu	Gln 110	Gln	Ala	
			115	Pro	Asp			120	Gln	Phe			125			Ala	
55		130					135			•		140				Leu	
	GII	cys	ser	THE	nen	ıyr	wid	rnr	GIN	ser	ser	ser	ABII	มอน	WTG	Glu	

148

	145					150					155					160
					Leu 165					170					175	
5	Ile	Asp	Val	His 180	Val	Leu	Ala	qaA	Ala 185	Phe	Lys	Arg	Tyr	Leu 190	Leu	Asp
	Leu	Pro	Asn 195	Pro	Val	Ile	Pro	Ala 200	Ala	Val	Tyr	Ser	Glu 205	Met	Ile	Ser
	Leu	Ala 210	Pro	Glu	Val	Gln	Ser 215	Ser	Glu	Glu	Tyr	Ile 220	Gln	Leu	Leu	Lys
10	<b>Lys</b> 225	Leu	Ile	Arg	Ser	Pro 230	Ser	Ile	Pro	His	Gln 235	Tyr	Trp	Leu	Thr	Leu 240
	Gln	Tyr	Leu	Leu	Lys 245	His	Phe	Phe	Lys	Leu 250	Ser	Gln	Thr	Ser	Ser 255	Lys
15	Asn	Leu	Leu	Asn 260	Ala	Arg	Val	Leu	Ser 265	Glu	Ile	Phe	Ser	Pro 270	Met	Leu
	Phe	Arg	Phe 275	Ser	Ala	Ala	Ser	Ser 280	Asp	Asn	Thr	Glu	Asn 285	Leu	Ile	Lys
	Val	Ile 290	Glu	Ile	Leu	Ile	Ser 295	Thr	Glu	Trp	Asn	Glu 300	Arg	Gln	Pro	Ala
20	Pro 305	Ala	Leu	Pro	Pro	Lys 310	Pro	Pro	Гув	Pro	Thr 315	Thr	Val	Ala	Asn	Asn 320
	Gly	Met	Asn	Asn	Asn 325	Met	Ser	Leu	Gln	Asn 330	Ala	Glu	Trp	Tyr	Trp 335	Gly
25	Asp	Ile	Ser	Arg 340	Glu	Glu	Val	Asn	Glu 345	Lys	Leu	Arg	Asp	Thr 350	Ala	Asp
	Gly	Thr	Phe 355	Leu	Val	Arg	Asp	Ala 360	Ser	Thr	Lys	Met	His 365	Gly	qaA	Tyr
	Thr	Leu 370	Thr	Leu	Arg	Lys	Gly 375	Gly	Asn	Asn	ГÀЗ	Leu 380	Ile	Lys	Ile	Phe
30	His 385	Arg	Asp	Gly	Lys	Tyr 390	Gly	Phe	Ser	Asp	Pro 395	Leu	Thr	Phe	Ser	Ser 400
	Val	Val	Glu	Leu	Ile 405	Asn	His	Tyr	Arg	Asn 410	Glu	Ser	Leu	Ala	Gln 415	Tyr
35	Asn	Pro	Lys	Leu 420	Asp	Val	Lys	Leu	Leu 425	Tyr	Pro	Val	Ser	Lys 430	Tyr	Gln
	Gln	Asp	Gln 435	Val	Val	ГÀв	Glu	Asp 440	Asn	Ile	Glu	Ala	Val 445	Gly	Lys	Lys
	Leu	His 450	Glu	Tyr	Asn	Thr	Gln 455	Phe	Gln	Glu	Lys	Ser 460	Arg	Glu	Tyr	Yab
40	465				Glu	470					475					480
	Arg	Thr	Ala	Ile	Glu 485	Ala	Phe	Asn	Glu	Thr 490	Ile	ГÀв	Ile	Phe	Glu 495	Glu
45	Gln	Cys	Gln	Thr 500	Gln	Glu	Arg	Tyr	Ser 505	Lys	Glu	Tyr	Ile	Glu 510	ГÀЗ	Phe
			515		Asn			520					525			
		530			Ser		535					540				
50	Leu 545		Glu	Asp	Leu	Lys 550	_	Gln	Ala	Ala	Glu 555		Arg	Glu	Ile	Asp 560
	_				Ser 565		_			570					575	
55	Arg	Asp	Gln	Tyr 580	Leu	Met	Trp	Leu	Thr 585		Lys	Gly	Val	Arg 590		Lys
	Tare	T.011	λen	Glu	Trans	Len	Glv	λen	Glu	Agn	Thr	Glu	Δan	Gln	TVY	Ser

			595					600					605			
	Leu	Val 610	Glu	Asp	Asp	Glu	Asp 615		Pro	His	His	Asp 620	Glu	Lys	Thr	Trp
5	625		Gly			630					635	Asn	Leu			640
	Lys	Arg	Asp	Gly	Thr 645	Phe	Leu	Val	Arg	Glu 650		Ser	Lys	Gln	Gly 655	Сув
			Cys	660					665					670	Val	
10			Thr 675					680					685			
		690	Leu				695					700				
15	705		Asn			710					715					720
			Arg		725					730					735	
			Leu	740					745					750		_
20			Asn 755					760					765			
		770	Tyr				775					780				
25	785		Val			790					795					800
			Phe		805					810				_	815	
			Ala	820					825					830		
30			Asp 835					840					845			_
		850	Leu				855					860				
35	865		Asn		•	870					875					880
			Tyr		885					890					895	
			Ile	900					905					910		
40			Gln 915					920					925			
		930	His				935					940				
45	945		Arg			950					Phe 955	Val	Thr	Ala	Ala	Gly 960
	Ile	Thr	Leu	Gly	Met 965	Asp	Glu	Leu	Tyr	Lув 970						
50								R SEC		NO : 6	8:					
		( i	) SE	CITER	ICE C	מסמדוי	ביתיים.	TOTI	ce.							

- (A) LENGTH: 1788 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- 55 (D) TOPOLOGY: linear

150

(ii) MOLECULE TYPE: cDNA (ix) FEATURE:

5

(A) NAME/KEY: Coding Sequence (B) LOCATION: 1...1785

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

		C	K1) 8	SEQUI	ENCE	DESC	CRIP.	LION	: SE(	Q ID	NO:	58:					
10								AAG Lys									48
15								AAG Lys									96
20								CAG Gln 40									144
25								GGG Gly									192
								ATG Met									240
30								CAC His									288
35								CTG Leu									336
40								GTC Val 120									384
45								ATT Ile									432
								GTC Val									480
50								CTG Leu									528
55	CAG Gln	CAG Gln	GGC Gly	TAT Tyr 180	ATT Ile	CAG Gln	GTG Val	ACA Thr	GAC Asp 185	TTC Phe	GG <b>T</b> Gly	TTT Phe	GCC Ala	AAG Lys 190	CGT Arg	GTG Val	576

151

		GGC Gly	Arg					Сув					Tyr				624
5			195					200					205				
3	GNG	ATT	איזיכי	CTC	»GC	מממ	cac	ሞልሮ	አአሮ	አአር	COT	CITICS	CNC	maa	maa	O CITT	670
		Ile															672
	014	210	110	пси	561	Буз	215	-7-	H211	пуъ	ATG	220	Mph	тър	rrb	ATG	
•												LLV					
10	CTC	GGA	GTC	CTC	ATC	TAC	GAG	ATG	GCT	GCT	GGT	TAC	CCA	CCC	TTC	TTC	720
		Gly															
	225					230					235	-				240	
		GAC															768
15	Ala	Asp	Gln	Pro	Ile	Gln	Ile	Tyr	Glu	Lys	Ile	Val	Ser	Gly	Lys	Val	
					245					250					255		
		TTC															816
20	Arg	Phe	PIO	260	uis	PHE	ser	ser	265	теп	гая	Asp	теп		Arg	Asn	
20				200					205					270			
	CTT	CTG	CAA	GTG	GAT	CTA	ACC	AAG	CGC	TTT	GGA	AAC	CTC	AAG	GAC	GGG	864
		Leu															
			275		_			280	•		1		285	•		<b>-</b>	
25																	
	GTC	TAA	GAC	ATC	AAG	AAC	CAC	AAG	TGG	TTT	GCC	ACG	ACT	GAC	TGG	ATT	912
	Val	Asn	Asp	Ile	Lys	Asn	His	Lys	$\mathtt{Trp}$	Phe	Ala	Thr	Thr	Asp	Trp	Ile	
		290					295					300			•		
20																	
30		ATC															960
	305	Ile	TYL	GIII	Arg	310	vaı	GIU	Ala	Pro	315	тте	Pro	гуя	Pue	ьуs 320	
	303					310					313					320	
	GGC	CCT	GGG	GAC	ACG	AGT	AAC	TTT	GAC	GAC	TAT	GAG	GAG	GAA	GAG	ATC	1008
35		Pro															
	_		-	-	325				•	330	•				335		
		GTC															1056
	Arg	Val	Ser		Asn	Glu	Lys	Сув	Gly	Lув	Glu	Phe	Thr	Glu	Phe	Gly	
40				340					345					350			
		~~~	<b>.</b>					~									
		GCC Ala															1104
	Arg	ATG	355	SEL	пув	GIY	GIU	360	Leu	Pne	THE	GIY	365	VAI	PLO	TTE	
45			درد					200					303				
	CTT	GTT	GAA	TTA	GAT	GGC	GAT	GTT	AAT	GGG	CAA	AAA	TTĊ	TCT	GTT	AGT	1152
		Val															
		370			_	-	375			•		380					
50		GAG															1200
	-	Glu	Gly	Glu	Gly	_	Ala	Thr	Tyr	Gly	-	Leu	Thr	Leu	Lys		
	385					390					395					400	
	y men	maa	3 CC	2 Carr	000	350	ALTER S	~~~	- Cheer	ac-	maa	~~	3.00		~m~	3 CITT	3740
55		TGC Cys															1248
00	716	Cla	TILL	****	405	פעני	neu	-10	VAL	410	тър	FTO	TIIT	пец	415	* ***	
										-10					-13		

	CTC Leu												1296
5	CAG Gln												1344
10	AGA Arg 450												1392
15	GTC Val												1440
20	ATT Ile												1488
25	AAT Asn												1536
<b>2</b> J	GGC Gly												1584
30	GTT Val 530												1632
35	CCT Pro												1680
40	TCC Ser												1728
45	GTA Val												1776
45	CAG Gln		TAA										1788
50		(2)	) INI	FORM	ATIO	ı FOI	R SE(	Q ID	NO:	59:			

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 595 amino acids
- 55 (B) TYPE: amino acid
  - (C) STRANDEDNESS: single

153

## (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

	Met 1	Gly	Asn	Ala	Ala 5	Ala	Ala	Lys	Lys	Gly 10	Ser	Glu	Gln	Glu	Ser 15	Val
10	Lys	Glu	Phe	Leu 20	Ala	ГÀВ	Ala	ГÀв	Glu 25	Asp	Phe	Leu	Lys	Lys 30	Trp	Glu
			35					40					45	Arg		
15		50					55					60		Lys		
	Glu 65	Ser	Gly	Asn	His	Tyr 70	Ala	Met	Lys	Ile	Leu 75	Asp	Lys	Gln	ГÀЗ	Val 80
	Val	Lys	Leu	Lys	Gln 85	Ile	Glu	His	Thr	Leu 90	Asn	Glu	ГÀв	Arg	Ile 95	Leu
20				100					105	-				Ser 110		-
	Asp	Asn	Ser 115	Asn	Leu	Tyr	Met	Val 120	Met	Glu	Tyr	Val	Ala 125	Gly	Gly	Glu
25		130					135		_	_		140		Pro		
	Arg 145	Phe	Tyr	Ala	Ala	Gln 150	Ile	Val	Leu	Thr	Phe 155	Glu	Tyr	Leu	His	Ser 160
	Leu	Asp	Leu	Ile	Tyr 165	Arg	Asp	Leu	Lys	Pro 170	Glu	Asn	Leu	Leu	Ile 175	Asp
30	Gln	Gln	Gly	Tyr 180	Ile	Gln	Val	Thr	Asp 185	Phe	Gly	Phe	Ala	Lys 190	Arg	Val
	Lys	Gly	Arg 195	Thr	Trp	Thr	Leu	Сув 200	Gly	Thr	Pro	Glu	Tyr 205	Leu	Ala	Pro
35		210					215			_		220	_	Trp	_	
	Leu 225	Gly	Val	Leu	Ile	Tyr 230	Glu	Met	Ala	Ala	Gly 235	Tyr	Pro	Pro	Phe	Phe 240
	Ala	qaA	Gln	Pro	Ile 245	Gln	Ile	Tyr	Glu	Lys 250	Ile	Val	Ser	Gly	Lys 255	Val
40	Arg	Phe	Pro	Ser 260	His	Phe	Ser	Ser	Asp 265	Leu	ГÀа	Asp	Leu	Leu 270	Arg	Asn
	Leu	Leu	Gln 275	Val	Asp	Leu	Thr	Lys 280	Arg	Phe	Gly	Asn	Leu 285	Lys	Asp	Gly
45	Val	Asn 290	Asp	Ile	Lys	Asn	His 295	rys	Trp	Phe	Ala	Thr 300	Thr	Asp	Trp	Ile
	Ala 305	Ile	Tyr	Gln	Arg	Lys 310	Val	Glu	Ala	Pro	Phe 315	Ile	Pro	ГÀв	Phe	Lys 320
	Gly	Pro	Gly	Asp	Thr 325	Ser	Asn	Phe	Asp	Asp 330	Tyr	Glu	Glu	Glu	Glu 335	Ile
50	Arg	Val	Ser	Ile 340	Asn	Glu	Lys	Cys	Gly 345	Lys	Glu	Phe	Thr	Glu 350	Phe	Gly
	Arg	Ala	Met 355	Ser	Lys	Gly	Glu	Glu 360	Leu	Phe	Thr	Gly	Val 365	Val	Pro	Ile
55	Leu	Val 370	Glu	Leu	Asp	Gly	Asp 375	Val	Asn	Gly	Gln	780 780	Phe	Ser	Val	Ser
	Gly		Gly	Glu	Gly	qaA		Thr	Tyr	Gly	ГÀв	Leu	Thr	Leu	Lys	Phe

	385					390					395					400	
					Gly 405					410	Trp				415	Thr	
5				420	Gly				425					430			
			435		Phe			440					445				
		450			Phe		455					460					
10	465				Glu	470					475					480	
					Lys 485					490					495		
15				500	Ser				505					510		_	
			515		Val			520					525				
20		530			Ala		535					540					
20	545				Leu	550					555					560	
					Pro 565					570					575		
25		Gln		580	Ala	GTÀ	TIE	Thr	H18 585	GΤΆ	Met	Asp	Glu	Leu 590	Tyr	Lys	
	710	GIII	595							٠							
30			(2)	IN	ORM?	TION	FOF	SE(	QI Ç	NO:7	70:						
		( 5			VCE (						•						
			(B)	TYPE	: nu	clei	.c ac	cid									
35					PLOGY				•								
				OLEC EATU	TULE TRE :	TYPE	: cI	NA									
40			(A)	NAM	IE/KE	Y: C	odir.	ıg Se	equer	ıce							
					ATIC ER I												
45		к)	ai) S	EQUE	NCE	DESC	RIPI	ON:	SEC	) ID	NO:7	0 :					
10	ATG	AGC	GAC	GTG	GCT	ATT	GTG	AAG	GAG	GGT	TGG	CTG	CAC	AAA	CGA	GGG	48
	1	per	Авр	vaı	Ala 5	116	Val	гÀ8	GIu	Gly 10	Trp	Leu	His	Lys	Arg 15	Gly	
50	GAG Glu	TAC	ATC	AAG	ACC	TGG	CGG	CCA	CGC	TAC	TTC	CTC	CTC	AAG	AAT	GAT	. 96
		-7-	110	20	Thr	ırp	Arg	PLU	25 25	туг	rne	ren	Leu	30 TAB	Asn	Asp	
55	GGC Glv	ACC Thr	TTC Phe	ATT	GGC Gly	TAC	AAG	GAG	CGG	CCG	CAG	GAT	GTG	GAC	CAA	CGT	144
-	1		35		~ <b>-</b> 1	-,-	~10	40	ALY	ETO	ĞTII	waħ	45	Asp	GIH	AT.G	

5	GAG Glu	GCT Ala 50	CCC Pro	CTC Leu	AAC Asn	AAC Asn	TTC Phe 55	TCT Ser	GTG Val	GCG Ala	CAG Gln	TGC Cya 60	CAG Gln	CTG Leu	ATG Met	AAG Lys	192
						CCC Pro 70											240
10						CGC Arg											288
15						GCC Ala											336
20						ATG Met											384
25						ATG Met											432
						TTT Phe 150											480
30						CTG Leu											528
35						AAG Lys											576
40						GAG Glu											624
45						AAG Lys											672
						GCC Ala 230				Glu							720
50						TCC Ser											768
55						GAC Asp											816

156

_		GAC Asp											864
5		ATC Ile 290											912
10		ATG Met											960
15		GAG Glu											1008
20		GTC Val											1056
25		CAT His	_										1104
·		CGC Arg 370											1152
30		AAG Lys											1200
35		ATC Ile											1248
40	_	GAG Glu		_	_	_		_		_	_		1296
45		GAC Asp		_	_		_	 	 	 		 	1344
		ACA Thr 450											1392
50		AGG Arg											1440
55		GAT Asp											1488

157

		GGG Gly								Leu							1536
5				500					505					510			
Ŭ	CAC	AAG	TTC	AGC	GTG	TCC	GGC	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	1584
		Lys															
		-	515				_	520	-		-	_	525		_	_	
10		CTG															1632
	ГÅв	Leu	Thr	Leu	Lys	Phe		Cys	Thr	Thr	Gly	-	Leu	Pro	Val	Pro	
		530					535					540					
	maa	ccc	700	CTC	dind	3,00	אככ	CTFC	700	מוא כו	aaa	CTC	CNG	TCC	ששכי	NGC	1680
15		Pro			_	_	_				_	_	_				1000
10	545	PLO	1111	neu	V (2.1.	550	1111	шсц	1111	T Y L	555	VAL	GIII	Cys	1 110	560	
	313																
	CGC	TAC	CCC	GAC	CAC	ATG	AAG	CAG	CAC	GAC	TTC	TTC	AAG	TCC	GCC	ATG	1728
	Arg	Tyr	Pro	Asp	His	Met	Lys	Gln	His	qaA	Phe	Phe	Lys	Ser	Ala	Met	
20					565					570					575		
		GAA							•								1776
	Pro	Glu	Gly	-	Val	Gin	Glu	Arg		Ile	Phe	Phe	Lys	_	Asp	GIA	
25				580					585					590			
25	אאכי	TAC	DAG	ACC	CGC	GCC	GAG	GTG	AAG	ттс	GAG	GGC	GAC	ACC	CTG	GTG	1824
		Tyr															
		-2-	595		-			600	•				605				
				•													
30		CGC															1872
	Asn	Arg	Ile	Glu	Leu	Lys		Ile	Asp	Phe	Lys		Asp	Gly	Asn	Ile	
		610					615					620					
	CTC	GGG	CAC	DAG	השגה	GAG	ሞልሮ	אאר	TAC'	מממ	AGC	CAC	AAC	מיזיכי	ייביי	ATC	1920
35		Gly															
	625	<b>-</b> -1		-1-		630	-1-		-2 -		635				-4-	640	
	ATG	GCC	GAC	AAG	CAG	AAG	AAC	GGÇ	ATC	AAG	GTG	AAC	TTC	AAG	ATC	CGC	1968
	Met	Ala	Asp	Lys	Gln	Lys	Asn	Gly	Ile	Lys	Val	Asn	Phe	Lys	Ile	Arg	
40					645					650					655		
				~~~	<b>~~</b>					~~~					~~~	ar a	2016
		AAC Asn															2016
	UTS	MBII	TTE	660	Map	GIY	SET	Val	665	пеп	MIG	Mah	ита	670	GIII	GIII	
45				<b></b>					203					5,5			
	AAC	ACC	CCC	ATC	GGC	GAC	GGC	CCC	GTG	CTG	CTG	CCC	GAC	AAC	CAC	TAC	2064
	Asn	Thr	Pro	Ile	Gly	Asp	Gly	Pro	Val	Leu	Leu	Pro	Asp	Asn	His	Tyr	
			675					680					685				
						_											
50		AGC															2112
	Leu	Ser	Thr	Gln	Ser	Ala			Lys	Asp	Pro		Glu	Lys	Arg	Asp	
		690					695					700					
	CAC	ATG	GTC	CTG	CTG	GAG	TTC	GTG	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	2160
55		Met															
	705					710				_	715					720	

158

ATG GAC GAG CTG TAC AAG TAA 2181 Met Asp Glu Leu Tyr Lys 725 5 (2) INFORMATION FOR SEQ ID NO:71: (i) SEQUENCE CHARACTERISTICS: 10 (A) LENGTH: 726 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 15 (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO.71: 20 Met Ser Asp Val Ala Ile Val Lys Glu Gly Trp Leu His Lys Arg Gly Glu Tyr Ile Lys Thr Trp Arg Pro Arg Tyr Phe Leu Leu Lys Asn Asp Gly Thr Phe Ile Gly Tyr Lys Glu Arg Pro Gln Asp Val Asp Gln Arg 25 Glu Ala Pro Leu Asn Asn Phe Ser Val Ala Gln Cys Gln Leu Met Lys 55 Thr Glu Arg Pro Arg Pro Asn Thr Phe Ile Ile Arg Cys Leu Gln Trp 75 30 Thr Thr Val Ile Glu Arg Thr Phe His Val Glu Thr Pro Glu Glu Arg 90 Glu Glu Trp Thr Thr Ala Ile Gln Thr Val Ala Asp Gly Leu Lys Lys 105 Gln Glu Glu Glu Met Asp Phe Arg Ser Gly Ser Pro Ser Asp Asn 35 120 Ser Gly Ala Glu Glu Met Glu Val Ser Leu Ala Lys Pro Lys His Arg 135 140 Val Thr Met Asn Glu Phe Glu Tyr Leu Lys Leu Leu Gly Lys Gly Thr . 150 155 40 Phe Gly Lys Val Ile Leu Val Lys Glu Lys Ala Thr Gly Arg Tyr Tyr 170 175 Ala Met Lys Ile Leu Lys Lys Glu Val Ile Val Ala Lys Asp Glu Val 185 Ala His Thr Leu Thr Glu Asn Arg Val Leu Gln Asn Ser Arg His Pro 45 195 200 Phe Leu Thr Ala Leu Lys Tyr Ser Phe Gln Thr His Asp Arg Leu Cys 215 220 Phe Val Met Glu Tyr Ala Asn Gly Gly Glu Leu Phe Phe His Leu Ser 230 235 50 Arg Glu Arg Val Phe Ser Glu Asp Arg Ala Arg Phe Tyr Gly Ala Glu 250 Ile Val Ser Ala Leu Asp Tyr Leu His Ser Glu Lys Asn Val Val Tyr 265 Arg Asp Leu Lys Leu Glu Asn Leu Met Leu Asp Lys Asp Gly His Ile

158

275 280 285 Lys Ile Thr Asp Phe Gly Leu Cys Lys Glu Gly Ile Lys Asp Gly Ala

		290					295					300				
	305		Lys			310					315					320
5			Asp		325					330					335	
	Val	Val	Met	Tyr 340	Glu	Met	Met	Сув	Gly 345		Leu	Pro	Phe	Tyr 350	Asn	Glr
	Asp	His	Glu 355	Lys	Leu	Phe	Glu	Leu 360	Ile	Leu	Met	Glu	Glu 365	Ile	Arg	Phe
10	Pro	Arg 370	Thr	Leu	Gly	Pro	Glu 375	Ala	Lys	Ser	Leu	Leu 380	Ser	Gly	Leu	Lev
	Lys 385	Lys	Asp	Pro	Lys	Gln 390	Arg	Leu	Gly	Gly	Gly 395	Ser	Glu	Asp	Ala	Lys 400
15	Glu	Ile	Met	Gln	His 405	Arg	Phe	Phe	Ala	Gly 410	Ile	Val	Trp	Gln	His 415	Val
	Tyr	Glu	ГÀв	Lys 420	Leu	Ser	Pro	Pro	Phe 425	Lys	Pro	Gln	Val	Thr 430	Ser	Glu
	Thr	Asp	Thr 435	Arg	Tyr	Phe	qeA	Glu 440	Glu	Phe	Thr	Ala	Gln 445	Met	Ile	Thr
20		450	Pro				455					460				
	Arg 465	Arg	Pro	His	Phe	Pro 470	Gln	Phe	Ser	Tyr	Ser 475	Ala	Ser	Ser	Thr	Ala 480
25			Pro		485					490					495	
			Val	500					505					510		
	His	Lys	Phe 515	Ser	Val	Ser	Gly	Glu 520	Gly	Glu	Gly	Asp	Ala 525	Thr	Tyr	Gly
30		530	Thr				535					540				
	545		Thr			550					555					560
35			Pro		565					570					575	
			Gly	580					585					590		
			Lys 595					600					605			
40		610	Ile				615					620				
	625		His			630					635					640
45			Asp		645					650					655	
			Ile	660					665	•				670		
			Pro 675					680					685			
50		690	Thr				695					700			_	
	705		Val			710	Phe	Val	Thr	Ala	Ala 715	Gly	Ile	Thr	Leu	Gly 720
55	Met	Asp	Glu	Leu	Tyr 725	Lys										

			(2)	INI	FORM	ATIO	1 FOI	SE(	QI C	NO: 7	72 :						
5		(:	(B)	LENC TYPI STRI	NCE ( GTH: E: nu ANDEI OLOGY	275: icle: ONES	l bas ic ac S: si	se pa cid ingle	airs								
10			ii) ! ix) !			TYPI	3: cI	AMC									
15			(B)	LO	ME/KI CATIO HER I	ON: 3	l2	2748	equer	ıce							
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:  ATG GCT GAC GTT TAC CCG GCC AAC GAC TCC ACG GCG TCT CAG GAC GTG  Met Ala Asp Val Tyr Pro Ala Asn Asp Ser Thr Ala Ser Gln Asp Val  1 5 10 15																
20	Met				Tyr					Ser					Asp		48
25																	96
		GTG Val															144
30		TGC Cys 50															192
35		CAG Gln															240
40		GTT Val															288
45		CCC Pro															336
-		TTC Phe															384
50		ATG Met 130															432
55		AAT Asn															480

					AAG Lys												528
5					165					170					175		
3	GTA	CGA	GAT	GCA	AAA	AAT	CTA	ATC	CCT	ATG	GAT	CCA	AAT	GGG	CTT	TCG	576
					Lys												
				100					105					190			
10					AAG												624
	чар	PIO	195	vai	Lys	ren	тув	200	TTE	PTO	Asp	Pro	1.уs 205	Asn	GIA	ser	
45					AAA												672
15	ГÀв	Gln 210	Lys	Thr	Lys	Thr	11e 215	Arg	Ser	Asn	Leu	220	Pro	Gln	Trp	Asn	
					TTC												720
20	Glu 225	Ser	Phe	Thr	Phe	Lys 230	Leu	Lys	Pro	Ser	Asp 235	Lys	Asp	Arg	Arg	Leu 240	
20	443					230					233					240	
		_	_	_	TGG												768
	ser	Val	GIT	He	Trp 245	Asp	Trp	Asp	Arg	Thr 250	Thr	Arg	Asn	Asp	Phe 255	Met	
25																	
					TTT												816
	GIA	ser	пец	260	Phe	GIY	vaı	ser	265	Leu	мес	гув	Met	270	ALA	ser	
30	GGA	TGG	TAT	AAA	GCT	CAC	AAC	CAA	GAA	GAG	GGC	GAA	TAT	TAC	AAC	GTG	864
			Tyr		Ala												
			275					280					285				
0.5		_			GGA												912
35	Pro	11e 290	Pro	Glu	Gly	Asp	Glu 295	Glu	Gly	Asn	Met	Glu 300	Leu	Arg	Gln	Lys	
					AAG												960
40		Glu	Lys	Ala	Lys		Gly	Pro	Val	Gly		Lys	Val	Ile	Ser		
40	305					310					315					320	
					AAG												1008
	Ser	Glu	Asp	Arg	Lys 325	Gln	Pro	Ser	Asn	Asn 330	Leu	Asp	Arg	Val	Lys 335	Leu	
45					323					330					233		
					TTC												1056
	Thr	Asp	Phe	Asn 340	Phe	Leu	Met	Val	Leu 345	Gly	Lys	Gly	Ser	Phe	Gly	Lys	
				320					323	•				330			
50					GAC												1104
	vai	мет	ьец 355	Ala	Asp	Arg	гÀŝ	360 GlA	Thr	Glu	Glu	Leu	Tyr 365	Ala	тте	гÀа	
					GAC												1152
55	Ile		Lys	Lys	qaA	Val		Ile	Gln	Asp	Asp		Val	Glu	Сла	Thr	
		370					375					380					

162

5		GTG Val				_											1200
-		CAG Gln															1248
10		GAA Glu															1296
15		AAA Lys															1344
20		GGA Gly 450															1392
25	Lys 465	CTG Leu	Asn	Asn	Val	Met 470	Leu	Asn	Ser	Glu	Gly 475	His	Ile	Lys	Ile	Ala 480	1440
	Asp	TTC Phe	Gly	Met	Суя 485	Lys	Glu	His	Met	Met 490	qaA	Gly	Val	Thr	Thr 495	Arg	1488
30		TTC Phe			_				_			_	_	_	_		1536
35		CCG Pro															1584
40		GAG Glu 530															1632
45		CTG Leu															1680
		TCC Ser															1728
50		GCC Ala															1776
55		CAT His							Asp					Glu		AGG Arg	1824

5	ATC Ile 610										1872
	TTT Phe										1920
10	CAG Gln										1968
15	TAT Tyr	_			_				_		2016
20	CGC Arg										2064
25	CTT Leu 690										2112
	 GGA Gly										2160
30	ATT Ile										2208
35	ACT Thr										2256
40	AAA Lys									_	2304
45	GAA Glu 770										2352
	GAA Glu						Asn				2400
50	GGT										2448
55	TAC Tyr		Asn			Tyr			Lys		2496

	AAG Lys												AAC Asn 845				2544
5	GGA Gly												ACT Thr				2592
10			•										TCC Ser				2640
15													ATG Met				2688
20													GAT Asp				2736
			CAG Gln 915		TAA								٠				2751
25			723														
			(2)	IN	FORM	ATIO	v FOI	R SE	O ID	ио:	73:						
30		(1	(B) (C)	EQUEI LENG TYPI STRI	GTH: G: at ANDE	916 mino DNES:	amin acid	no ad i ingle	cids								
35			ii) ! /) Fl				_										
		(:	ci) !	SEQU	ENCE	DES	CRIP'	TION	: SE	Q ID	NO:	73:					
40	1				5					10			Ser		15		
	Ala	Asn	Arg	Phe 20	Ala	Arg	Lys	Gly	Ala 25	Leu	Arg	Gln	ГЛЗ	Asn 30	Val	His	
45	Glu	Val	Lys 35	Asp	His	Lys	Phe	Ile 40	Ala	Arg	Phe	Phe	Lув 45	Gln	Pro	Thr	
	Phe	Cys 50	Ser	His	Cys	Thr	Asp 55	Phe	Ile	Trp	Gly	Phe 60	Gly	Lys	Gln	Gly	
	Phe 65		Сув	Gln	Val	Cys		Phe	Val	Val	His		Arg	Cys	His	Glu 80	
50		Val	Thr	Phe	Ser 85		Pro	Gly	Ala	Asp		Gly	Pro	Asp	Thr 95	Asp	
	Авр	Pro	Arg	Ser	Lys	His	Lys	Phe	Lys 105	Ile	His	Thr	Tyr	Gly		Pro	
55	Thr	Phe	Сув 115	Asp		Сув	Gly	Ser	Leu		туг	Gly	Leu 125	Ile		Gln	
55	Glv	Met			Asp	Thr	Cvs			Asr	. Val	. Hie			. Сув	. Val	

		130					135					140				
	Ile 145	Asn	Asp	Pro	Ser	Leu 150		Gly	Met	Asp	His 155		Glu	Lys	Arg	Gly 160
. 5	Arg	Ile	Tyr	Leu	Lys 165	Ala	Glu	Val	Thr	Asp 170	Glu	ГÀв	Leu	His	Val 175	Thr
	Val	Arg	Asp	Ala 180	FÀR	Asn	Leu	Ile	Pro 185	Met	Asp	Pro	Asn	Gly 190	Leu	Ser
	Asp	Pro	Tyr 195	Val	Lys	Leu	ГЛя	Leu 200	Ile	Pro	Asp	Pro	Lув 205	Asn	Glu	Ser
10	-	210	rya		-		215	_				220			_	
	Glu 225	Ser	Phe	Thr	Phe	Lys 230	Leu	ГÀа	Pro	Ser	Asp 235	Lys	qaA	Arg	Arg	Leu 240
15	Ser	Val	Glu	Ile	Trp 245	Asp	Trp	Asp	Arg	Thr 250	Thr	Arg	Asn	qaA	Phe 255	Met
	=		Leu	260					265					270		
	_	_	Tyr 275	_				280			-		285	_		
20		290	Pro		_		295		_			300		_		_
	305		Lys		_	310	_			_	315	-				320
25			Asp		325					330		-			335	
		_	Phe	340					345	-	-	-		350	_	-
			Leu 355		_		_	360					365			
30		370	ГÀв				375				-	380				
	385		Glu	_	_	390					395	-				400
35			Leu		405	_				410	_			_	415	
			Tyr	420			-	_	425		_			430		
			Phe 435	_				440			_		445			
40		450	Leu				455			_		460	_			
	465		Asn			470					475					480
45			Gly		485					490	-	_			495	
			СЛа	500				_	505					510		
			Tyr 515					520		_		_	525			
50		530	Met				535				_	540				
	545		Phe			550					555					560
55			- FÀB		565					570					575	
	Dro	777	Tare	7 200	T.OII	Clar	C310	(2) 110	Dva	Clu	G 137	(3 1 11	Ara	Λοη	Val	Arc

166

```
585
                                                         590
                 580
     Glu His Ala Phe Phe Arg Arg Ile Asp Trp Glu Lys Leu Glu Asn Arg
                                600
                                                    605
     Glu Ile Gln Pro Pro Phe Lys Pro Lys Val Cys Gly Lys Gly Ala Glu
5
                   615
     Asn Phe Asp Lys Phe Phe Thr Arg Gly Gln Pro Val Leu Thr Pro Pro
                        630
                                            635
      Asp Gln Leu Val Ile Ala Asn Ile Asp Gln Ser Asp Phe Glu Gly Phe
                     645
                                        650
10
     Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val
                 660
                                     665
      Gly Arg Ala Met Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro
                                680
      Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly Gln Lys Phe Ser Val
15
                            695
                                       . 700
      Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys
                                            715
                         710
      Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val
                     725
                                        730
20
      Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His
                                     745
      Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val
                                 760
      Gln Glu Arg Thr Ile Phe Tyr Lys Asp Asp Gly Asn Tyr Lys Thr Arg
25
                             775
      Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu
                         790
      Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met
                                         810
      Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Pro
30
                                     825
      Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Lys Asp
      Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly
35
                             855
      Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser
                         870
                                             875
      Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Ile Leu Leu
                     885
                                         890
40
      Glu Phe Val Thr Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr
                 900
                                     905
      Lys Pro Gln Glu
              915
45
               (2) INFORMATION FOR SEQ ID NO:74:
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 2157 base pairs
              (B) TYPE: nucleic acid
50
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: cDNA
            (ix) FEATURE:
```

(A) NAME/KEY: Coding Sequence

167

(B) LOCATION: 1...2154 (D) OTHER INFORMATION:

(xi)	SEQUENCE	DESCRIPTION:	SEQ ID	NO:74:
------	----------	--------------	--------	--------

5		()	ci) S	EQUE	ENCE	DESC	RIPT	: NOI	SEC	ID	NO: 7	74 :					
J	ATG	TCG	TCC	ATC	TTG	CCA	TTC	ACG	CCG	CCA	GTT	GTG	AAG	AGA	CTG	CTG	48
						Pro											
	1				5					10				_	15		
40																	
10						GCT			_								96
	СТУ	тъ	пуъ	шу <b>Б</b> 20	SEL	Ala	GIY	GTA	25	GIY	GIY	ALA	GTÀ	30	GTÀ	GIU	
									45					30			
						GAA											144
15	Gln	Asn		Gln	Glu	Glu	Lys	Trp	Сув	Glu	ГÀЗ	Ala	Val	Lys	Ser	Leu	
			35					40					45				
	GTG	AAG	AAG	CTA	AAG	AAA	ACA	GGA	CGA	тта	GAT	GAG	СТТ	GAG	AAA	GCC	192
						Lys											
20		50	_		_		55	_	_		_	60			_		
						TGT											240
	65	THE	TIII	GIII	WBII	Cys 70	MBII	Int	гув	Сув	75	THE	116	PLO	ser	80	
25											, 5						
	TGC	TCT	GAA	ATT	TGG	GGA	CTG	AGT	ACA	CCA	AAT	ACG	ATA	GAT	CAG	TGG	288
	Сув	Ser	Glu	Ile	_	Gly	Leu	Ser	Thr	Pro	Asn	Thr	Ile	qaA		Trp	
					85					90 .					95		
30	GAT	ACA	ACA	GGC	CTT	TAC	AGC	TTC	тст	GAD	CAA	ACC	AGG	тст	СТТ	GAT	336
						Tyr											
	_			100		_			105				_	110		_	
35						TCC											384
33	GIY	ALG	115	GIII	Val	Ser	HTR	120	гув	GIA	Leu	PIO	125	vaı	TTE	Tyr	
								220					123				
	TGC	CGA	TTA	TGG	CGC	TGG	CCT	GAT	CTT	CAC	AGT	CAT	CAT	GAA	CTC	AAG	432
	Сув	_	Leu	Trp	Arg	Trp	Pro	qaA	Leu	His	Ser	His	His	Glu	Leu	Lys	
40		130					135					140					
	GCA	ATT	GAA	AAC	TGC	GAA	TAT	GCT	بلململ	דעם	היחה	ΔΔΔ	DAG	GAT	AAD	GTA	480
						Glu											
	145				-	150	-				155	-	-	_		160	
45																	
						CAC											528
	Сув	val	ASII	Pro	191 165	His	Tyr	GIN	Arg	170	GIU	THE	PIO	vaı	175	PIO	
										_,,					2		
50						CGA											576
	Pro	Val	Leu		Pro	Arg	His	Thr	Glu	Ile	Leu	Thr	Glu	Leu	Pro	Pro	
				180					185					190			
	ርጥር	GAT	GAC	TAT	אַניייי	CAC	TCC	Δጥጥ	CCA	GAA	אאר	אריידי	אארי	יויתי	CCA	GCA	624
55						His											
		-	195	-				200					205				

	GGA	ATT	GAG	CCA	CAG	AGT	AAT	TAT	ATT	CCA	GAA	ACG	CCA	CCT	CCT	GGA	672
	Gly	Ile	Glu	Pro	Gln	Ser	Asn	Tyr	Ile	Pro	Glu		Pro	Pro	Pro	Gly	
_		210					215					220					
5			3 CM	<b>~~</b> ~ ~	an m	003	C1 N N	אמא	AGT	מאמ	מא	CAG	ጥጥር፤	דממ	CAA	AGT	720
	TAT	ATC	AGT	GAA	Dan	GUA	GAA	Thr	Ser	Asp	Gln	Gln	Leu	Asn	Gln	Ser	
	225	TIE	SEL	Giu	rop	230	014	1111		p	235					240	
	223																
10	ATG	GAC	ACA	GGC	TCT	CCA	GCA	GAA	CTA	TCT	CCT	ACT	ACT	CTT	TCC	CCT	768
	Met	Asp	Thr	Gly	Ser	Pro	Ala	Glu	Leu	Ser	Pro	Thr	Thr	Leu	Ser	Pro	
					245					250					255		
									~~~	amm.	<b>.</b>	m > 0	mas	<b>733</b>	CCT	CCN	816
4	GTT	AAT	CAT	AGC	TTG	GAT	TTA	CAG	CCA	GTT	ACT	TAC	Cor	GAA	Dro	Mla	010
15	Val	Asn	His		Leu	qaA	ьeu	GIN	Pro 265	var	THE	TAT	Ser	270	FIG	ALU	
				260					203								
	սեսեսե	TGG	TGT	TCA	ATA	GCA	TAT	TAT	GAA	TTA	AAT	CAG	AGG	GTT	GGA	GAA	864
	Phe	Trp	Cys	Ser	Ile	Ala	Tyr	Tyr	Glu	Leu	Asn	Gln	Arg	Val	Gly	Glu	
20		-	275					280					285				
																	0.0
									CTC								912
	Thr		His	Ala	Ser	Gln		Ser	Leu	Thr	Val		GIĀ	Pne	Thr	Asp	
25		290					295					300					
25	CCA	יירים	דממ	тсъ	GAG	AGG	TTC	TGC	TTA	GGT	TTA	CTC	TCC	AAT	GTT	AAC	960
									Leu								
	305					310		•		•	315					320	
30									AGA								1008
	Arg	Asn	Ala	Thr		Glu	Met	Thr	Arg		His	Ile	GTA	Arg	335	vai	
					325					330					333		
	רפר	מידיים	ጥልሮ	ТΔС	ΔΤΔ	GGT	GGG	GAA	GTT	TTT	GCT	GAG	TGC	CTA	AGT	GAT	1056
35									Val								
	5			340		•	•		345				_	350			
																TGG	1104
	Ser	Ala			Val	Gln	Ser			Сув	Asn	Gln			GIY	Trp	
40			355					360					365				
	מאמ	COT	GCN	ארא	CTC	יייבייי	מממ	דייד ב	י ררש	CCA	GGC	тст	TAA	CTG	AAG	ATC	1152
	His	Pro	Ala	Thr	Val	Cvs	Lvs	Ile	Pro	Pro	Glv	Cys	Asn	Leu	Lys	Ile	
	1120	370				-1-	375				•	380					
45																	
	TTC	AAC	AAC	CAG	GAA	TTT	GCI	GC3	CTI	CTG	GCI	CAG	TCI	GTI	raa '	CAG	1200
	Phe	Asn	. Asn	Gln	Glu			Ala	Lev	Let			Ser	Va]	. Asr	Gln	•
	385	i				390	1				395	5				400	
EO		, mm-	. ~~	, ,,,,,	, cime	יאות ו	י מאר	. cm	י אירים	י אכיי	<b>ኒ</b> አጥረ	ייים ב	י אריר	יית י	AGZ	ATG	1248
50																Met	
	GTÀ	FILE	. 346	. MIC	405		, 311	اناب	_ +	410		J-			419		
						-											
	AGT	r TT	r GTC	AA E	A GGC	TGC	GG/	A GC	A GAZ	A TAC	C CG	A AGO	G CAC	ACC	GT?	A ACA	1296
55	Ser	Phe	e Val	L Lys	Gly	Tr	Gly	/ Ala	a Gli	ту:	r Ar	g Arg	g Glı			LThr	
				420	)				429	5				430	כ		

PCT/DK98/00145

							<b></b>	omm.	G3.00	oma	* * *	aa s	CCT	OTT N	CNG	TCC.	1344
		ACT Thr															1344
5											•						
		GAC Asp 450															1392
10		ATG Met															1440
	465	Mec	DC1.	110	Val	470	****		1119	p	475					480	
		AGC															1488
15	Val	Ser	ras '	Gly	Glu 485	Glu	Leu	Phe	Thr	Gly 490	Val	Val	Pro	Ile	Leu 495	Val	
		CTG															1536
20	Glu	Leu	Asp	Gly 500	qaA	Val	Asn	Gly	His 505	rys	Phe	Ser	Val	Ser 510	Gly	Glu	
	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	CTG	ACC	CTG	AAG	TTC	ATC	TGC	1584
	Gly	Glu	Gly 515	Asp	Ala	Thr	Tyr	Gly 520	Lys	Leu	Thr	Leu	Lys 525	Phe	Ile	Cys	
25							ama		maa		3.00	ama	ama	3.00	3.00	CTPC	1632
		ACC Thr															1032
		530	,	-1-			535					540					
30		TAC															1680
	Thr 545	Tyr	Gly	Val	Gln	Cys 550	Phe	Ser	Arg	Tyr	Pro 555	Asp	His	Met	гàв	560	
		GAC															1728
35	His	Asp	Phe	Phe	<b>Lys</b> 565	Ser	Ala	Met	Pro	Glu 570	Gly	Tyr	Val	Gln	Glu 575	Arg	
	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	GTG	1776
40	Thr	Ile	Phe	Phe 580	Lys	Asp	Asp	Gly	Asn 585	Tyr	Lys	Thr	Arg	Ala 590	Glu	Val	
	AAG	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAC	CGC	ATC	GAG	CTG	AAG	GGC	ATC	1824
	Lys	Phe		Gly	Asp	Thr	Leu	Val 600		Arg	Ile	Glu	Leu 605		Gly	Ile	
45	•		595					800					003				
																AAC	1872
	Asp	Phe 610	_	Glu	Asp	Gly	Asn 615		Leu	Gly	' His	620		GLu	. тух	Asn	
50																: GGC	1920
	Tyr 625		Ser	His	Asn	Val 630		Ile	: Met	Ala	Asp 635		Gln	Lys	Asr	Gly 640	
	ATC	AAG	GTG	AAC	TTC	AAG	ATC	: CGC	CAC	. AAC	ATC	GAG	GAC	: GGC	AGC	GTG	1968
55	Ile	Lys	Val	. Asn			Ile	Arg	His			Glu	Asp	Gly	' Sez 655	val	
					645					650	,				955	•	

	CAG C	TC G	la A	BAC (Asp )	CAC His	TAC Tyr	CAG Gln	Gln	AAC Asn 665	ACC Thr	CCC :	ATC	GTA Y	SAC Asp	GGC (	CCC Pro	2016
5	GTG C	eu I	יידים (	CC	GAC Asp	AAC Asn	CAC His	TAC Tyr 680	CTG Leu	AGC Ser	ACC Thr	CAG Gln	TCC ( Ser ) 685	GCC Ala	CTG Leu	AGC Ser	2064
10	AAA G	AC ( Asp )	ccc ; Pro ;	AAC Asn	GAG Glu	AAG Lys	CGC Arg 695	GAT Asp	CAC His	ATG Met	GTC Val	CTG Leu 700	CTG Leu	GAG Glu	TTC Phe	GTG Val	2112
15	ACC C Thr A	SCC (	GCC (	Gly	ATC Ile	ACT Thr 710	CTC Leu	GGC Gly	ATG Met	GAC Asp	GAG Glu 715	CTG Leu	TAC Tyr	AAG Lys	TAA		2157
20		(i						R SE(			75 :						
25			(B) (C)	TYPE	: at	nino ONES	aci S: s	ingl									
								rote tern									
30		(x	i) S	EQUI	ENCE	DES	CRIF	TION	: SE	Q ID	NO:	75:					•
	Met 1				5					10					15		
35	Gly			20					25				Gly	30			
			35					40					Val 45				
	Val	Lys 50	Lys	Leu	ГÀв	Ьys	Thi 55	Gly	Arg	J Leu	Asp	Glu 60	Leu	GLU	. ràs	Ala	
40		Thr	Thr	Gln	Asn	. Cys	Ası	1 Thr	Lys	сув	Val	Thr	Ile	Pro	Ser	Thr 80	
	65 Cys	Ser	Glu	Ile	Trp 85	Gly	Le	ı Ser	Thi	Pro		Thr	Ile	Asp	Gln 95	Trp	
AE	Asp	Thr	Thr	Gly 100	Lev	туз	Se	r Phe	Se:		ı Glr	Th:	Arg	Ser 110	Lev	Asp	
45	Gly	Arg	Leu 115	Gln	. Val	. Se	: Hi	в Arg 120	J Ly		/ Let	ı Pro	His 125	Va]		Tyr	
	Сув	Arg	Leu	Trp	Arg	j Trj	Pro	o Asj		u His	s Sei	c Hi:	s His	Glu	ı Let	ı Lys	
50		Ile	Glu	Ası	суя	3 Gli 15		r Ala	a Ph	e Ası	n Let 15!	ı Ly:	s Lys	Asj	o Glu	Val 160	
	145 Cys	Val	Asn	Pro		r Hi		r Gl	n Ar		1 Gl		r Pro	Va:	1 Let	ı Pro	
	Pro	Val	Leu	ı Val	16! Pro	o Ar	g Hi	s Th				u Th	r Glu	1 Le	u Pr	o Pro	
55	Leu	Asp	Asr	180 Ty:	). r Th	r Hi	s Se	r Il	18 e Pr		u As	n Th	r Ası			o Ala	

			195					200					205			
		210	Glu				215	Tyr				220				
_	Tyr	Ile	Ser	Glu		Gly 230	Glu	Thr	Ser	Asp	Gln 235	Gln	Leu	Asn	Gln	Ser 240
5	225 Met	qeA	Thr	Gly	Ser		Ala	Glu	Leu	Ser 250		Thr	Thr	Leu	Ser 255	Pro
	Val	Asn	His		245 Leu	Asp	Leu	Gln	Pro 265		Thr	Tyr	Ser			Ala
10	Phe	Trp		260 Ser	Ile	Äla	Tyr	Tyr 280		Leu	Asn	Gln	Arg 285		Gly	Glu
	Thr		275 His	Ala	Ser	Gln	Pro 295	Ser	Leu	Thr	Val	Asp 300		Phe	Thr	Asp
15	Pro 305	290 Ser	Asn	Ser	Glu	Arg 310		Сув	Leu	Gly	Leu 315		Ser	Asn	Val	Asn 320
13	Arg	Asn	Ala	Thr	Val 325		Met	Thr	Arg	Arg 330	His	Ile	Gly	Arg	Gly 335	Val
	Arg	Leu	Tyr	Tyr 340		Gly	Gly	Glu	Val 345	Phe	Ala	Glu	Cys	Leu 350	Ser	Asp
20			355					Pro 360					365			
		370	Ala				375					380				
25	385	Asn				390		Ala			395					400
	Gly				405			Leu		410					415	
				420				Ala	425					430		
30			435					Leu 440					445			
		450					455					460				
35	465					470		Ala			475					480
					485			Phe		490	•				495	
				500				Gly	505					510		
40			515	;				Gly 520					525			
		530	)				535					540	)			
45	545					550	+	ser			555	i				560
					565			Met		570	)				575	5
				580	)			Gly	585	5				590	)	
50			595	5				val 600	)				605	5		
	_	610	)				61					62	0			
55	625	;				630	)	r Ile e Arg			63	5				640
	116	· LiV	ы Val.	L ABI		- 41/2	- 11			o Mö.					,	

										14								
				(	545					650					555			
	Gln 1	Leu .			His '	I'yr	Gln (			Thr	Pro	Ile	Gly	Asp ( 670	3TA I	ro		
	Val 1	.e.1	T.en 1	660 Pro 2	Asp i	Asn	His '		665 Leu	Ser	Thr	Gln			Leu S	er		
5			675					680					685					
	Lys i			Asn (	Glu :			Asp	His	Met	Val	Leu 700	Leu	Glu 1	Phe V	Val		
	Thr 2	690.	בות	Glv '	Tle '		695 Leu	Glv	Met	Asp			Tyr	Lys				
	705	nia	ALG.	<b>-</b>		710		1		•	715		-	_				
10																		
			(2)	INF	ORMA	TION	FOR	SEC	iπ	NO: /	<b>6</b> :							
		i)	.) SE	QUEN	CE C	HARA	CTER	ISTI	CS:									
				LENG					irs									
15				TYPE STRA					<u>.</u>									
				TOPO					-									
20			li) M lx) F			TABE	: CL	INA			•							
20		\ -	Lac, L															
				NAM					equei	ıce								
				LOC								•						
25																		
		(:	ki) S	EQUE	ENCE	DESC	CRIP	CION	: SE	) ID	NO:	76:						
	ATG	GAC	AAT	ATG	TCT	ATT	ACG	AAT	ACA	CCA	ACA	AGT	AAT	GAT	GCC	TGT	48	
	Met	Asp	Asn	Met	Ser	Ile	Thr	Asn	Thr	Pro	Thr	Ser	Asn	Asp	Ala	Cys		
30	1.				5					10					15			
	CTG	AGC	ATT	GTG	CAT	AGT	TTG	ATG	TGC	CAT	AGA	CAA	GGT	GGA	GAG	AGT	96	
	Leu	Ser	Ile	Val	His	Ser	Leu	Met	Сув	His	Arg	Gln	Gly	Gly	Glu	Ser		
35				20					25					30				
33	GAA	ACA	TTT	GCA	AAA	AGA	GCA	ATT	GAA	AGT	TTG	GTA	AAG	AAG	CTG	AAG	144	
	Glu	Thr		Ala	Lys	Arg	Ala		Glu	Ser	Leu	Val		Lys	Leu	ГÀЗ		
			35					40					45					
40	GAG	AAA	AAA	GAT	GAA	TTG	GAT	TCT	TTA	ATA	ACA	GCI	ATA	ACT	ACA	AAT	192	
	Glu		Lys	Asp	Glu	Leu	Asp 55	Ser	Leu	Ile	Thr	Ala 60	Ile	Thr	Thr	Asn		
		50					23											
	GGA	GCT	CAT	CCT	AGT	AAA	TGT	GTI	ACC	ATA	CAG	AGP	ACA	TTG	GAT	GGG	240	
45	_	Ala	His	Pro	Ser	Lys 70	Сув	Val	Thr	Ile	: Gln 75	Arg	Thr	Leu	Asp	80 GTA		
	65					70												
	AGG	CTI	CAG	GTG	GCT	GGT	CGG	AAA	GGA	TII	CCI	CA	GTO	ATC	TAT	GCC	288	
50	Arg	Leu	Gln	Val	Ala 85	Gly	Arg	Lys	GLY	Phe 90	Pro	HI	a val	Ile	95	AIG		
50																		
	CGT	CTC	TGG	AGG	TGG	CCI	GAT	CTT	CAC	: AA	AA A	GA	A CT	AAA	CAT	GTT V=1	336	
	Arg	Let	1 Trp	Arg		Pro	ASE	ь цег	1 His		s Asi	1 G1	т тел	1 Lys 110		AGT		
55																		
	AAA	TA?	r TGI	CAG	TAT	GCC	TT	GA(	TTI	AA A	A TG	r GA	r ag'	r GTC	TGT	GTG	384	170
																		172

	Lys	Tyr	Cys 115	Gln	Tyr	Ala	Phe	Asp 120	Leu	Lys	Сув	Asp	Ser 125	Val	Сув	Val	
	AAT	CCA	TAT	CAC	TAC	GAA	CGA	GTT	GTA	TCA	CCT	GGA	ATT	GAT	CTC	TCA	432
5		Pro 130															
	GGA	TTA	ACA	CTG	CAG	AGT	AAT	GCT	CCA	TCA	АСТ	ATG	АТС	GTG	AAG	GAT	480
		Leu															100
10	145					150					155				-	160	
		TAT															528
15	Glu	Tyr	Val	His	165	Phe	Glu	Gly	Gln	Pro 170	Ser	Leu	Ser	Thr	GLu 175	GIA	
15	CAT	TCA	יניניע	ממי	»cc	איזיכי	CAG	ርስጥ	CCA	רכא	ልርም	דממ	CGT	GCZ	ጥሮር	מרמ	576
		Ser															3,0
20		ACA															624
	GIU	Thr	195	ser	Thr	Pro	ATA	200	ren	ATA	Pro	ser	205	ser	Asn	AIA	
	ACC	AGC	ACT	GCC	AAC	TTT	CCC	AAC	ATT	CCT	GTG	GCT	TCC	ACA	AGT	CAG	672
25	Thr	Ser 210	Thr	Ala	Asn	Phe	Pro 215	Asn	Ile	Pro	Val	Ala 220	Ser	Thr	Ser	Gln	
	دري	GCC	AGT	ата	CTG	GGG	GGC	AGC	CAT	AGT	GAA	GGA	CTG	TTG	CAG	ATA	720
		Ala															
30	225					230					235					240	
	GCA	TCA	GGG	CCT	CAG	CCA	GGA	CAG	CAG	CAG	AAT	GGA	TTT	ACT	GGT	CAG	768
	Ala	Ser	Gly	Pro	Gln	Pro	Gly	Gln	Gln	Gln	Asn	Gly	Phe	Thr	Gly	Gln	
35					245					250					255		
33	CCA	GCT	ACT	TAC	CAT	CAT	AAC	AGC	ACT	ACC	ACC	TGG	ACT	GGA	AGT	AGG	816
		Ala															
•				260					265					270			
40	ACT	GCA	CCA	TAC	ACA	CCT	AAT	TTG	CCT	CAC	CAC	CAA	AAC	GGC	CAT	CTT	864
	Thr	Ala	Pro 275	Tyr	Thr	Pro	Asn	Leu 280		His	His	Gln	Asn 285	Gly	His	Leu	
	CAG	CAC	CAC	CCG	CCT	ATG	CCG	CCC	CAT	CCC	GGA	CAT	TAC	TGG	CCT	GTT	912
45																Val	
		290					295				_	300	_				
																CCT	960
			Glu	Leu	Ala			Pro	Pro	Ile			His	Pro	Ala	Pro	
50	305					310					315					320	
																GGA	1008
	Glu	Tyr	Trp	Cys			Ala	Tyr	Phe			Asp	Val	Gln		Gly	
55					325					330	•				335	•	
JJ	GAG	ACA	TTT	AAG	GTI	CCT	TCA	AGC	TGC	CCI	ATT	GTI	ACT	GTI	GAT	GGA	1056

									•	174							
	Glu	Thr	Phe	Lys 340	Val	Pro	Ser	Ser	Cys 345	Pro	Ile	Val	Thr	Val 350	Asp	Gly	
<b>5</b> .												TTG Leu					1104
10												AGG Arg 380					1152
												GAT Asp					1200
15												TAC Tyr					1248
20												AAG Lys					1296
25		Tyr										CAT His					1344
30												GCC Ala 460					1392
												GGT Gly					1440
35												GTT Val					1488
40												GGC					1536
45				Gln					Thr			TGG Trp		Glu			1584
50			Arg					Leu					His			CCG Pro	1632
		Ala					Leu					Pro				ATG Met 560	1680
55	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	. ACC	GGG	GTG	GTG	cco	ATC	CTG	GTC	1728

										113							
	Val	Ser	Lys	Gly	Glu 565	Glu	Leu	Phe	Thr	Gly 570		Val	Pro	Ile	Leu 575	Val	
	GAG	CTG	GAC	GGC	GAC	CTD	ልልሮ	aac	CAC	AAG	ጥጥር	AGC	ana	שרר	ccc	GAG	1776
5		Leu															1770
Ū	GIU	Deu	nap	580	Nop	vai	ABII	GLY	585	цув	FIIC	DCI	Val	590	Cly	<b>314</b>	
	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	CTG	ACC	CTG	AAG	TTC	ATC	TGC	1824
	Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	Cys	
10			595					600					605				
		ACC															1872
	Thr	Thr	Gly	Lys	Leu	Pro		Pro	Trp	Pro	Thr		Val	Thr	Thr	Leu	
		610					615					620					
15																	
		TAC															1920
		Tyr	GTA	Val	Gin	_	Phe	Ser	Arg	Tyr		Asp	H18	Met	Lys		
	625					630					635					640	
20	CA C	CZC	חידירי	TTTC	220	TOO	aca	א יישר א	ccc	C 7 7	aac	ሞአሮ	GTTC	CAC	CAC	cac	1968
20		GAC Asp															7300
	пть	Asp	FIIC	FIIC	645	561	AIG	Mec	FIO	650	Gry	TYL	VAI	GIII	655	my.	
					043					050					033		
	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TÁC	AAG	ACC	CGC	GCC	GAG	GTG	2016
25		Ile															
				660	-	-	-	-	665	-	-		_	670			
											•						
	AAG	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAC	CGC	ATC	GAG	CTG	AAG	GGC	ATC	2064
	Lys	Phe	Glu	Gly	Авр	Thr	Leu	Val	Asn	Arg	Ile	Glu	Leu	Lys	Gly	Ile	
30			675					680					685				
		TTC															2112
	Asp	Phe	Lys	Glu	Asp	Gly		Ile	Leu	Gly	His	-	Leu	Glu	Tyr	Asn	
25		690					695					700					
35	m= a			a. a					3 000	-	~~		a. a	***	220	000	2160
		AAC															2160
	705	Asn	ser	HIR	ASII		TAT	тте	met	Ald	_	пλя	GIII	пув	Wall	720	
	705					710					715					720	
40	ATC	AAG	GTG	AAC	יייניים	מממ	ATC	CGC	ראכ	AAC	ATC	GAG	GAC	GGC	AGC	GTG	2208
		Lys							-								
					725	-1-				730				1	735		
	CAG	CTC	GCC	GAC	CAC	TAC	CAG	CAG	AAC	ACC	CCC	ATC	GGC	GAC	GGC	CCC	2256
45	Gln	Leu	Ala	Asp	His	Tyr	Gln	Gln	Asn	Thr	Pro	Ile	Gly	Авр	Gly	Pro	
				740		-			745					750			
	GTG	CTG	CTG	CCC	GAC	AAC	CAC	TAC	CTG	AGC	ACC	CAG	TCC	GCC	CTG	AGC	2304
	Val	Leu	Leu	Pro	Asp	Asn	His	Tyr	Leu	Ser	Thr	Gln	Ser	Ala	Leu	Ser	
50			755					760					765				
																GTG	2352
	Lys	Asp	Pro	Asn	Glu	Lys		_	His	Met	۷al			Glu	Phe	Val	
cc		770					775					780					
55	אממ	CCC	GOO	gaa	አጥር	), com	CMC	000	» ma	ana	GN C		י אידי	አክጣ	ጥአጽ		2397
	ACC	GCC	GCC	فاتان	ATC	ACT	CTC	GGC	ATG	GAC	GAG	, C16	IAC	AAG	TAA	•	
																	17

176

Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 785 790 795

5 (2) INFORMATION FOR SEQ ID NO:77:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 798 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

15

55

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

Met Asp Asn Met Ser Ile Thr Asn Thr Pro Thr Ser Asn Asp Ala Cys 10 20 Leu Ser Ile Val His Ser Leu Met Cys His Arg Gln Gly Glu Ser Glu Thr Phe Ala Lys Arg Ala Ile Glu Ser Leu Val Lys Lys Leu Lys 40 Glu Lys Lys Asp Glu Leu Asp Ser Leu Ile Thr Ala Ile Thr Thr Asn 25 55 Gly Ala His Pro Ser Lys Cys Val Thr Ile Gln Arg Thr Leu Asp Gly 70 75 Arg Leu Gln Val Ala Gly Arg Lys Gly Phe Pro His Val Ile Tyr Ala 85 90 30 Arg Leu Trp Arg Trp Pro Asp Leu His Lys Asn Glu Leu Lys His Val 105 Lys Tyr Cys Gln Tyr Ala Phe Asp Leu Lys Cys Asp Ser Val Cys Val 120 115 Asn Pro Tyr His Tyr Glu Arg Val Val Ser Pro Gly Ile Asp Leu Ser 35 135 140 Gly Leu Thr Leu Gln Ser Asn Ala Pro Ser Ser Met Met Val Lys Asp 150 155 Glu Tyr Val His Asp Phe Glu Gly Gln Pro Ser Leu Ser Thr Glu Gly 170 40 His Ser Ile Gln Thr Ile Gln His Pro Pro Ser Asn Arg Ala Ser Thr 185 Glu Thr Tyr Ser Thr Pro Ala Leu Leu Ala Pro Ser Glu Ser Asn Ala 200 Thr Ser Thr Ala Asn Phe Pro Asn Ile Pro Val Ala Ser Thr Ser Gln 45 215 220 Pro Ala Ser Ile Leu Gly Gly Ser His Ser Glu Gly Leu Leu Gln Ile 230 235 Ala Ser Gly Pro Gln Pro Gly Gln Gln Asn Gly Phe Thr Gly Gln 250 50 Pro Ala Thr Tyr His His Asn Ser Thr Thr Thr Trp Thr Gly Ser Arg 265 Thr Ala Pro Tyr Thr Pro Asn Leu Pro His His Gln Asn Gly His Leu

176

275 280 285
Gln His His Pro Pro Met Pro Pro His Pro Gly His Tyr Trp Pro Val

His Asn Glu Leu Ala Phe Gln Pro Pro Ile Ser Asn His Pro Ala Pro

										177						
	305					310					315					320
	Glu	Tyr	Trp	СЛа	Ser 325	Ile	Ala	Tyr	Phe	Glu 330	Met	Asp	Val	Gln	Val 335	Gly
5	Glu	Thr	Phe	Lys 340		Pro	Ser	Ser	Сув 345		İle	Val	Thr	Val 350		Gly
	Tyr	Val	Asp 355	Pro	Ser	Gly	Gly	Asp 360		Phe	Cys	Leu	Gly 365		Leu	Ser
	Asn	Val 370	His	Arg	Thr	Glu	Ala 375		Glu	Arg	Ala	Arg 380		His	Ile	Gly
10	Lys 385		Val	Gln	Leu	Glu 390		Lys	Gly	Glu	Gly 395		Val	Trp	Val	Arg 400
	Сув	Leu	Ser	Asp	His 405	Ala	Val	Phe	Val	Gln 410	Ser	Tyr	Tyr	Leu	Asp 415	Arg
15	Glu	Ala	Gly	Arg 420	Ala	Pro	Gly	qaA	Ala 425	Val	His	Lys	Ile	Tyr 430	Pro	Ser
	Ala	Tyr	Ile 435	Lys	Val	Phe	Asp	Leu 440	Arg	Gln	Cys	His	Arg 445	Gln	Met	Gln
	Gln	Gln 450	Ala	Ala	Thr	Ala	Gln 455	Ala	Ala	Ala	Ala	Ala 460	Gln	Ala	Ala	Ala
-20	Val 465	Ala	Gly	Asn	Ile	Pro 470	Gly	Pro	Gly	Ser	Val 475	Gly	Glÿ	Ile	Ala	Pro 480
	Ala	Ile	Ser	Leu	Ser 485	Ala	Ala	Ala	Gly	Ile 490	Gly	Val	Asp	Asp	Leu 495	Arg
25	Arg	Leu	Сув	Ile 500	Leu	Arg	Met	Ser	Phe 505	Val	Lys	Gly	Trp	Gly 510	Pro	Asp
	Tyr	Pro	Arg 515	Gln	Ser	Ile	Lys	Glu 520	Thr	Pro	Cys	Trp	Ile 525	Glu	Ile	His
	Leu	His 530	Arg	Ala	Leu	Gln	Leu 535	Leu	Asp	Glu	Val	Leu 540	His	Thr	Met	Pro
30	Ile 545	Ala	Asp	Pro	Gln	Pro 550	Leu	Asp	Trp	Asp	Pro 555	Pro	Val	Ala	Thr	Met 560
	Val	Ser	Lув	Gly	Glu 565	Glu	Leu	Phe	Thr	Gly 570	Val	Val	Pro	Ile	Leu 575	Val
35			Asp	580	_			-	585	-				590	-	
			Gly 595					600					605			
		610	Gly				615					620				
40	625		Gly			630					635					640
					645					650	-	_			655	Arg
45	•			660					665	_				670		Val
			675					680					685			Ile
50		690					695			_		700				Asn
50	705					710	_				715	_		_		Gly 720
			Val		725			_		730					735	
.55				740					745					750		Pro
	AdT	T-CIT	TICH	FIG	voh	wait	UTB	⊥y <i>⊑</i>	LEU	ber	TIIT	GTII	act	wrd	nen	Ser

									1	78									
			755			_	_	760			<b>-</b>	_	765						
	Lys	Asp 770	Pro	Asn	Glu	ГÀЗ	Arg 775	Asp	His	Met	Val	Leu 780	Leu	Glu	Phe	Val			
-		Ala	Ala	Gly	Ile		Leu	Gly	Met	Asp		Leu	Tyr	Lys					
5	785					790					795								
			(2)	INF	'ORMA	TION	FOR	SEQ	ID	NO:7	8:								
		(i	.) SE	QUEN	CE C	HARA	CTER	ISTI	CS:										
10				LENG				-	irs										
				TYPE					:										
			(D)	TOPO	LOGY	: li	near	•											
15		(i	.i) M	OLEC	ULE	TYPE	: cE	NA											
		(i	.x) I	EATU	RE:														
				NAM	-			_	quen	ce									
-20			(B) (D)	LOC TOTE	ATIC ER -1	N: 1 NFOR	L3 RMATI	135 ON:											:
		()	(1) 8	EQUE	ENCE	DESC	:RIP1	: NOT:	SEC	) TD	NO:	/8:							
25		GCG Ala															4	8	
25	1	AIA	СΤΆ	тгЪ	5	GIII	Ala	GIII	GIII	10	GIII	СТУ	Asp	AIG	15	мg			
	CZG	ATG	CVG	GTG.	ריזונו	ТАС	GGC	CAG	CAC	ጥጥሮ	CCC	ATC	GAG	GTC	CGG	CAC	9	96	
		Met		Val					His					Val					
30				20					25					30					
		TTG															14	14	
	туг	Leu	35	GIN	Trp	TIE	GTÜ	40	GIII	PIO	11þ	Asp	45	TTE	wah	Бец			
35	GAC	AAT	ccc	CAG	GAC	AGA	GCC	CAA	GCC	ארירי	CAG	CTC	CTG	GAG	GGC	CTG	19	92	
		Asn					Ala					Leu							
		50					55					60							
40		CAG															24	40	
	Val	Gln	GIU	Leu	GIn	ьув 70	ràs	АТА	GIU	нів	75 75	vaı	GIĀ	GIU	Asp	80 GTA			
	mmm	CONTRACTOR AND AND AND AND AND AND AND AND AND AND	- CITIC!	አአሮ	N.M.CT	እአሮ	CITIC	aaa	מאמ	מיז כי	aca	אכפ	CVC	CTC	CAG	AAA	2:	88	
45		Leu															2		
					85					90					95				
																ATT	3	36	
50	Thr	Tyr	Asp	Arg 100	Cys	Pro	Leu	Glu	Leu 105	Val	Arg	Сув	Ile	Arg 110		Ile			
					<b>a</b> a	200	ama	ama			~~~			maa	».dd	man	. 3	0.4	
																TCT Ser	3	84	
		•	115			_		120	_				125						
55	CCG	GCT	GGG	ATC	CTG	GTT	GAC	GCC	ATG	TCC	CAG	AAG	CAC	CTI	CAC	ATC	4	32	
																		•	178

									•	179							
	Pro	Ala 130	Gly	Ile	Leu	Val	Asp 135	Ala	Met	Ser	Gln	Lys 140	His	Leu	Gln	Ile	
5				TTT Phe													480
10				AAA Lys													528
				CTG Leu 180													576
15				GAG Glu													624
20				GAG Glu													672
25				GAG Glu													720
30				CAG Gln													768
35				CAG Gln 260													816
				CAG Gln													864
40				CAG Gln					_								912
45	_			CCA Pro								Val			_	_	960
50				ATC Ile		Ala										Lys	1008
55				CAG Gln 340	Val					Thr					Thr	GTA Val	1056
	CGC	CTG	CTG	GTG	GGC	GGG	AAG	CTG	AAC	GTG	CAC	ATG	AAT	ccc	ccc	CAG	1104

•										180							
	Arg	Leu	Leu 355	Val	Gly	Gly	Lys	Leu 360	Asn	Val	His	Met	Asn 365	Pro	Pro	Gln	
5					ATC Ile										-		1152
10					CGC Arg												1200
15					TAC Tyr 405												1248
19					CTG Leu												1296
20					GAG Glu	_									_	_	1344
25					AAT Asn				-								1392
30 .					ATC Ile											_	1440
35					GAC Asp 485												1488
JJ					AAA Lys												1536
40					GCC Ala												1584
45					CTG Leu												1632
50					AGT Ser												1680
55					GGC Gly 565											GGG Gly	1728
- <b>-</b>	GTG	ATG	GAG	GTG	TTG	AAG	AAG	CAC	CAC	AAG	CCC	CAC	TGG	AAT	GAT	GGG	1776

181

										181							*
	Val	Met	Glu	Val 580	Leu	Гуз	ГÀЗ	His	His 585	Lys	Pro	His	Trp	Asn 590	Asp	Gly	
5					TTT Phe												1824
10					GGG	Thr											1872
15					ATC Ile												1920
15					CCA Pro 645												1968
20					GGG Gly												2016
25					GAG Glu												2064
30					GGA Gly												2112
35					GCA Ala												2160
33					CCC Pro 725												2208
40					AAC Asn												2256
45					ACC Thr												2304
50					GAC Asp												2352
55					GCC Ala												2400
- '	GAT	CCA	CCG	GTC	GCC	ACC	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	2448

										182						•	
	qaA	Pro	Pro	Val	Ala 805	Thr	Met	Val	Ser	<b>L</b> ув 810	Gly	Glu	Glu	Leu	Phe 815	Thr	
5												GAC Asp					2496
10												GCC Ala					2544
45												CTG Leu 860					2592
15												CAG Gln					2640
20												AAG Lys					2688
25												AAG Lys					2736
30												GAC Asp					2784
												GAC Asp 940					2832
35												AAC Asn					2880
40												TTC Phe					2928
45					Gly					Ala					Gln	AAC Asn	2976
50							Pro		Leu			Asp		His		CTG Leu	3024
	Ser		Gln			Leu		Lys					Lys			CAC His	3072
55	ATG	GTC	CTG	CTG	GAG	TTC	GTG	ACC	GCC	GCC	: GGG	ATC	ACT	CTC	: GGC	: ATG	3120

183

Met Val Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met 1035 GAC GAG CTG TAC AAG TAA 3138 5 Asp Glu Leu Tyr Lys 1045 (2) INFORMATION FOR SEQ ID NO:79: 10 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 1045 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single 15 (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:79: Met Ala Gly Trp Ile Gln Ala Gln Gln Leu Gln Gly Asp Ala Leu Arg Gln Met Gln Val Leu Tyr Gly Gln His Phe Pro Ile Glu Val Arg His 25 Tyr Leu Ala Gln Trp Ile Glu Ser Gln Pro Trp Asp Ala Ile Asp Leu 40 Asp Asn Pro Gln Asp Arg Ala Gln Ala Thr Gln Leu Leu Glu Gly Leu 30 Val Gln Glu Leu Gln Lys Lys Ala Glu His Gln Val Gly Glu Asp Gly 75 Phe Leu Leu Lys Ile Lys Leu Gly His Tyr Ala Thr Gln Leu Gln Lys 90 Thr Tyr Asp Arg Cys Pro Leu Glu Leu Val Arg Cys Ile Arg His Ile 35 105 Leu Tyr Asn Glu Gln Arg Leu Val Arg Glu Ala Asn Asn Cys Ser Ser 120 Pro Ala Gly Ile Leu Val Asp Ala Met Ser Gln Lys His Leu Gln Ile 135 140 Asn Gln Thr Phe Glu Glu Leu Arg Leu Val Thr Gln Asp Thr Glu Asn 40 150 155 Glu Leu Lys Lys Leu Gln Gln Thr Gln Glu Tyr Phe Ile Ile Gln Tyr 165 170 Gln Glu Ser Leu Arg Ile Gln Ala Gln Phe Ala Gln Leu Ala Gln Leu 45 180 185 Ser Pro Gln Glu Arg Leu Ser Arg Glu Thr Ala Leu Gln Gln Lys Gln 200 Val Ser Leu Glu Ala Trp Leu Gln Arg Glu Ala Gln Thr Leu Gln Gln 215 50 Tyr Arg Val Glu Leu Ala Glu Lys His Gln Lys Thr Leu Gln Leu Leu 230 235 Arg Lys Gln Gln Thr Ile Ile Leu Asp Asp Glu Leu Ile Gln Trp Lys 245 250 Arg Arg Gln Gln Leu Ala Gly Asn Gly Gly Pro Pro Glu Gly Ser Leu 55 265 Asp Val Leu Gln Ser Trp Cys Glu Lys Leu Ala Glu Ile Ile Trp Gln

			275					280					285			
	Asn	Arg 290	Gln	Gln	Ile	Arg	Arg 295	Ala	Glu	His	Leu	Сув 300	Gln	Gln	Leu	Pro
	Ile	Pro	Gly	Pro	Val	Glu	Glu	Met	Leu	Ala	Glu	Val	Asn	Ala	Thr	Ile
5	305					310					315					320
					325					330				Ile	335	-
	Gln	Pro	Pro	Gln 340	Val	Leu	Lys	Thr	Gln 345	Thr	Lys	Phe	Ala	Ala 350	Thr	Val
10	Arg	Leu	Leu 355	Val	Gly	Gly	Lys	Leu 360	Asn	Val	His	Met	Asn 365	Pro	Pro	Gln
	Val	Lys 370	Ala	Thr	Ile	Ile	Ser 375	Glu	Gln	Gln	Ala	Lys 380	Ser	Leu	Leu	Lys
	Asn	Glu	Asn	Thr	Arg	Asn	Glu	Сув	Ser	Gly	Glu	Ile	Leu	Asn	Asn	Сув
15	385					390					395					400
•	Суз	Val	Met	Glu	Tyr 405	His	Gln	Ala	Thr	Gly 410	Thr	Leu	Ser	Ala	His 415	Phe
	Arg	Asn	Met	Ser 420	Leu	Lys	Arg	Ile	Lys 425	Arg	Ala	Asp	Arg	Arg 430	Gly	Ala
20			435					440					445	Ser		
		450					455					460		Leu		
	Pro	Val	Val	Val	Ile		His	Gly	Ser	Gln		His	Asn	Ala	Thr	Ala
25	465		_	_	_	470			_ =		475				_	480
					485					490				Val	495	
				500				-	505			_		Ala 510		
30			515					520			_	-	525	Thr	=	
		530					535					540		Ser		
35	Leu 545	Glu	Asp	Tyr	Ser	Gly 550	Leu	Ser	Val	Ser	Trp 555	Ser	Gln	Phe	Asn	Arg 560
					565	-		_		570	_		_	Phe	575	_
				580					585					Asn 590		
40			595					600					605	Leu		
	Asn	Lys 610	Pro	qaA	Gly	Thr	Phe 615	Leu	Leu	Arg	Phe	Ser 620	Asp	Ser	Glu	Ile
45	Gly 625	Gly	Ile	Thr	Ile	Ala 630	Trp	Lys	Phe	Asp	Ser 635	Pro	Glu	Arg	Asn	Leu 640
	Trp	Asn	Leu	ГÀЗ	Pro 645	Phe	Thr	Thr	Arg	Asp 650	Phe	Ser	Ile	Arg	Ser 655	Leu
	Ala	Asp	Arg	Leu 660	Gly	Asp	Leu	Ser	Tyr 665	Leu	Ile	Tyr	Val	Phe 670	Pro	Asp
50	Arg	Pro	Lув 675	Asp	Glu	Val	Phe	Ser 680	Lys	Tyr	Tyr	Thr	Pro 685	Val	Leu	Ala
		690					695	_				700		Val		
		Phe	Val	Asn	Ala		Ala	Asp	Ala	Gly	Gly	Ser	Ser	Ala	Thr	Tyr
55	705	_			_	710	_	_ =			715					720
	Met	Asn	Gln	Ala	Pro	Ser	Pro	Δla	Wal	Cva	Pro	Gln	Ala	Pro	ጥጥ	Agr

185

										100						
					725					730					735	
	Met	Tyr	Pro	Gln 740	Asn	Pro	Asp	His	Val 745	Leu	Asp	Gln	qaA	Gly 750		Phe
5	Asp	Leu	Asp 755	Glu	Thr	Met	Asp	Val 760	Ala	Arg	His	Val	Glu 765	Glu	Leu	Leu
	Arg	Arg 770	Pro	Met	Авр	Ser	Leu 775	Asp	Ser	Arg	Leu	Ser 780		Pro	Ala	Gly
	Leu 785	Phe	Thr	Ser	Ala	Arg 790	Gly	Ser	Leu	Ser	Trp 795	Val	Pro	Arg	Ala	Arg 800
10	Asp	Pro	Pro	Val	Ala 805	Thr	Met	Val	Ser	Lys 810	•	Glu	Glu	Leu	Phe 815	
	Gly	Val	Val	Pro 820	Ile	Leu	Val	Glu	Leu 825	Asp	Gly	Asp	Val	Asn 830	Gly	His
15	rys	Phe	Ser 835	Val	Ser	Gly	Glu	Gly 840	Glu	Gly	Asp	Ala	Thr 845	Tyr	Gly	Lys
	Leu	Thr 850	Leu	Lys	Phe	Ile	Cys 855	Thr	Thr	Gly	Lys	Leu 860	Pro	Val	Pro	Trp
	Pro 865	Thr	Leu	Val	Thr	Thr 870	Leu	Thr	Tyr	Gly	Val 875	Gln	Сув	Phe	Ser	Arg 880
20	Tyr	Pro	Asp	His	Met 885	ГÀВ	Gln	His	Asp	Phe 890	Phe	Lys	Ser	Ala	Met 895	Pro
	Glu	Gly	Tyr	Val 900	Gln	Glu	Arg	Thr	Ile 905	Phe	Phe	Lys	Asp	Asp 910	Gly	Asn
25	Tyr	Lys	Thr 915	Arg	Ala	Glu	Val	Lys 920	Phe	Glu	Gly	Asp	Thr 925	Leu	Val	Asn
	Arg	Ile 930	Glu	Leu	Lys	Gly	Ile 935	qaA	Phe	Lys	Glu	Asp 940	Gly	Asn	Ile	Leu
	945	His				950					955					960
30		Asp			965					970					975	
		Ile		980					985					990		
35		Pro	995				:	1000				1	L005			
	:	Thr 1010				:	1015	_			:	L020	-	_	_	
	025	Val			:	Phe L030	Val	Thr	Ala		Gly 1035	Ile	Thr	Leu		Met 1040
40	Asp	Glu			1045				٠							
45				IN						NO:	BO:					
45		(:	(A) (B) (C)	LENC TYPI STRI	GTH: E: n: ANDE	28 l icle: ONES:	base ic ad S: s:	pai: cid ingle	rs							
50																
		(:	xi) :	SEQU	ENCE	DES	CRIP'	rion	: SE	Q ID	NO:	80:				

(2) INFORMATION FOR SEQ ID NO:81:

TGGGATCCTC AGGCCGTGCT GCTGGCCG

55

185

5	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 27 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:	
	GTCTCGAGGG AGCATGGGCA CCTTGCG	27
	(2) INFORMATION FOR SEQ ID NO:82:	
15	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 27 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>	·
20	(D) TOPOLOGY: linear	
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:	
	TGGGATCCGA GAAGTCTATA TCCCATC	27
25	(2) INFORMATION FOR SEQ ID NO:83:	
30	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 28 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
35	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:	
	TGGGATCCTT AGAAGTCTAT ATCCCATC	28
40	(2) INFORMATION FOR SEQ ID NO:84:	
40	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 28 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
45	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(x1) SEQUENCE DESCRIPTION: SEQ ID NO:84:	
50	GTCTCGAGCC ATGAACGCCC CCGAGCGG	28
	(2) INFORMATION FOR SEQ ID NO:85:	
55	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 30 base pairs  (B) TYPE: nucleic acid	

	107	
	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:	
	GTGAATTCTC GTCTGATTTC TGGCAGGAGG	30
10	(2) INFORMATION FOR SEQ ID NO:86:	
10	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 30 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
15	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:	
20	GTGAATTCTT TACGTCTGAT TTCTGGCAGG	30
	(2) INFORMATION FOR SEQ ID NO:87:	
25	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 34 base pairs  (B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:	
	GTCTCGAGCC ATGGACGAAC TGTTCCCCCT CATC	34
35	(2) INFORMATION FOR SEQ ID NO:88:	
	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 31 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
40	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:	
40	GTGGATCCAA GGAGCTGATC TGACTCAGCA G	31
	(2) INFORMATION FOR SEQ ID NO:89:	
50	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 32 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single	
55	(D) TOPOLOGY: linear	

	188	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:	
	GTGGATCCTT AGGAGCTGAT CTGACTCAGC AG	32
5	(2) INFORMATION FOR SEQ ID NO:90:	
10	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 32 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:	
15	CCTCCTAAGC TTATCATGGA CCATTATGAT TC	32
	(2) INFORMATION FOR SEQ ID NO:91:	
20	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 33 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>	
25	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:	
	CCTCCTGGAT CCCTGCGCAG GATGATGGTC CAG	33
30	(2) INFORMATION FOR SEQ ID NO:92:	
35	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 45 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:	
	GGATGGAAGC TTCAATGGCT GCCATCCGGA AGAAACTGGT GATTG	45
45	(2) INFORMATION FOR SEQ ID NO:93:	
45	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 45 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>	
50	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:	
55	GGATGGGGAT CCTCACAAGA CAAGGCAACC AGATTTTTC TTCCC	45

	109	
	(2) INFORMATION FOR SEQ ID NO:94:	
5	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 29 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:	
	GGGAAGCTTC CATGAGCGAG ACGGTCATC	29
15	(2) INFORMATION FOR SEQ ID NO:95:	
20	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 28 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:	
25	CCCGGATCCT CAGGGAGAAC CCCGCTTC	28
	(2) INFORMATION FOR SEQ ID NO:96:	
30	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 30 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
35		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:	
	GTGAATTCGA CCATGGAGCG GCCCCCGGGG	30
40	(2) INFORMATION FOR SEQ ID NO:97:	
•	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs	
45	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
50	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:	
,	GTGGTACCCA TTCTGTTAAC CAACTCC	27
	(2) INFORMATION FOR SEQ ID NO:98:	
55	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs	

	190	
	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:	
	GTGGTACCTC ATTCTGTTAA CCAACTCC	28
10	(2) INFORMATION FOR SEQ ID NO:99:	
15	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 28 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:	
20	GTCTCGAGAG ATGCTGTCCC GTGGGTGG	28
	(2) INFORMATION FOR SEQ ID NO:100:	
25	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 27 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>	
30	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:	
	GTGAATTCGC TTCCTCTTGA GGGAACC	27
35	(2) INFORMATION FOR SEQ ID NO:101:	
40	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 27 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:	
	GTGAATTCAC TTCCTCTTGA GGGAACC	27
50	(2) INFORMATION FOR SEQ ID NO:102:	
	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 29 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>	
55	(D) TOPOLOGY: linear	

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:	
5	GTCTCGAGCC ATGGAGAACT TCCAAAAGG	29
J	(2) INFORMATION FOR SEQ ID NO:103:	
10	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 28 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
15	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:	
	GTGGATCCCA GAGTCGAAGA TGGGGTAC	28
20	(2) INFORMATION FOR SEQ ID NO:104:	
20	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 29 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>	
25	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:	
30	GTGGATCCTC AGAGTCGAAG ATGGGGTAC	29
	(2) INFORMATION FOR SEQ ID NO:105:	
35	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 30 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:	
	GTGAATTCGG CGATGCCAGA CCCCGCGGCG	30
45	(2) INFORMATION FOR SEQ ID NO:106:	
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs	
50	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
CE	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:	
55	GTGGATCCCA GGCACAGGCA GCCTCAGCCT TC	32 191

192

.

	(2) INFORMATION FOR SEQ ID NO:107:		
5	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 33 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>		
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:		
	GTGGATCCTC AGGCACAGGC AGCCTCAGCC TTC		33
15	(2) INFORMATION FOR SEQ ID NO:108:		
	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 2616 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>		
20	(C) STRANDEDNESS: single (D) TOPOLOGY: linear		
OF	(ii) MOLECULE TYPE: cDNA (ix) FEATURE:		
25	<ul><li>(A) NAME/KEY: Coding Sequence</li><li>(B) LOCATION: 12613</li><li>(D) OTHER INFORMATION:</li></ul>		
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:		
35	ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro 1 5 10		48
33	GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val 20 25 30		96
40	GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys 35 40 45		144
45	TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val 50 55 60		192
50	CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His 65 70 75		240
S.E.	CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val		288
55	CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC	GCC GAG	336 192

					•				-	193		-				•	
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105		Tyr	Lys	Thr	Arg 110	Ala	Glu	
5									GTG Val								384
10									ATC Ile								432
15									ATC Ile								480
•									CGC Arg								528
20									CAG Gln 185								576
25								-	TAC Tyr								624
30									GAT Asp								672
35									GGC Gly								720
									TCG Ser								768
40									GGC Gly 265								816
45									ATG Met					Phe			864
50	_						_		GGC Gly								912
55									ATC Ile								960
<b>5</b> 5	TAC	GCC	ATT	GCC	GGC	GGC	AAA	GCG	CAC	TGT	GGA	CCG	GCA	GAG	CTC	TGC	1008

										194							
	Tyr	Ala	Ile	Ala	Gly 325	Gly	Lys	Ala	His	Cys 330		Pro	Ala	Glu	Leu 335	Cys	
5	GAG Glu	TTC Phe	TAC Tyr	TCG Ser 340	CGC Arg	GAC Asp	CCC Pro	GAC Asp	GGG Gly 345	CTG Leu	CCC	TGC Cys	AAC Asn	CTG Leu 350	CGC Arg	AAG Lys	1056
10	CCG Pro	TGC Cys	AAC Asn 355	CGG Arg	CCG Pro	TCG Ser	GGC Gly	CTC Leu 360	GAG Glu	CCG Pro	CAG Gln	CCG Pro	GGG Gly 365	GTC Val	TTC Phe	GAC Asp	1104
15	Сув	Leu 370	Arg	GAC Asp	Ala	Met	Val 375	Arg	Asp	Tyr	Val	Arg 380	Gln	Thr	Trp	Lys	1152
	CTG Leu 385	GAG Glu	GGC Gly	GAG Glu	GCC Ala	CTG Leu 390	GAG Glu	CAG Gln	GCC Ala	ATC Ile	ATC Ile 395	AGC Ser	CAG Gln	GCC Ala	CCG Pro	CAG Gln 400	1200
20	GTG Val	GAG Glu	AAG Lys	CTC Leu	ATT Ile 405	GCT Ala	ACG Thr	ACG Thr	GCC Ala	CAC His 410	GAG Glu	CGG Arg	ATG Met	CCC Pro	TGG Trp 415	TAC Tyr	1248
25	CAC His	AGC Ser	AGC Ser	CTG Leu 420	ACG Thr	CGT Arg	GAG Glu	GAG Glu	GCC Ala 425	GAG Glu	CGC Arg	AAA Lys	CTT Leu	TAC Tyr 430	TCT Ser	GGG Gly	1296
30	GCG Ala	CAG Gln	ACC Thr 435	GAC Asp	GGC Gly	AAG Lys	TTC Phe	CTG Leu 440	CTG Leu	AGG Arg	CCG Þro	CGG Arg	AAG Lys 445	GAG Glu	CAG Gln	GGC Gly	1344
35	ACA Thr	TAC Tyr 450	GCC Ala	CTG Leu	TCC Ser	CTC Leu	ATC Ile 455	TAT Tyr	GGG Gly	AAG Lys	ACG Thr	GTG Val 460	TAC Tyr	CAC His	TAC Tyr	CTC Leu	1392
	ATC Ile 465	AGC Ser	CAA Gln	GAC Asp	AAG Lys	GCG Ala 470	GGC Gly	AAG Lys	TAC Tyr	TGC Cys	ATT Ile 475	CCC Pro	GAG Glu	GGC Gly	ACC Thr	AAG Lys 480	1440
40	TTT Phe	GAC Asp	ACG Thr	CTC Leu	TGG Trp 485	CAG Gln	CTG Leu	GTG Val	GAG Glu	TAT Tyr 490	CTG Leu	AAG Lys	CTG Leu	AAG Lys	GCG Ala 495	GAC Asp	1488
45	GGG	CTC Leu	ATC Ile	TAC Tyr 500	TGC Cys	CTG Leu	AAG Lys	GAG Glu	GCC Ala 505	TGC Cys	CCC Pro	AAC Asn	AGC Ser	AGT Ser 510	GCC Ala	AGC Ser	1536
50	AAC Asn	GCC Ala	TCA Ser 515	GGG Gly	GCT Ala	GCT Ala	GCT Ala	CCC Pro 520	ACA Thr	CTC Leu	CCA Pro	GCC Ala	CAC His 525	CCA Pro	TCC Ser	ACG Thr	1584
55	TTG Leu	ACT Thr 530	CAT His	CCT Pro	CAG Gln	AGA Arg	CGA Arg 535	ATC Ile	GAC Asp	ACC Thr	CTC Leu	AAC Asn 540	TCA Ser	GAT Asp	GGA Gly	TAC Tyr	1632
	ACC	CCT	GAG	CCA	GCA	CGC	ATA	ACG	TCC	CCA	GAC	AAA	CCG	CGG	CCG	ATG	1680

										195							
	Thr 545	Pro	Glu	Pro	Ala	Arg 550	Ile	Thr	Ser	Pro	Asp 555	ГÀЗ	Pro	Arg	Pro	Met 560	
5					AGC Ser 565												1728
10					AAG Lys												1776
15					GGC Gly												1824
13					AAG Lys												1872
20					AAG Lys									_			1920
25			_		CTG Leu 645												1968
30					GCC Ala												2016
25					TTC Phe												2064
35					CTG Leu												2112
40					TTT Phe								-				2160
45					CAC His 725												2208
50					GAC Asp												2256
EE					TGG Trp									Arg			2304
55	TCC	AGC	CGC	AGC	GAT	GTC	TGG	AGC	TAT	GGG	GTC	ACC	ATG	TGG	GAG	GCC	2352

					•				-	196		•				•	
	Ser	Ser 770	Arg	Ser	Asp	Val	Trp 775	Ser	Tyr	Gly	Val	Thr 780	Met	Trp	Glu	Ala	
5			TAC Tyr														2400
10			TTC Phe														2448
15			GAA Glu														2496
			CGC Arg 835														2544
20			AGC Ser														2592
25			GAG Glu					TGA									2616
30		(i	i) SI	INI EQUEN	NCE (	CHARA	CTE	RIST	CS:	NO:	L09:						
35			(B) (C)	TYPI STRA	E: an	nino ONESS	ació S: si	l ingle									
			ii) N /) FF				-										
40		()	(i) 5	SEQUI	ENCE	DESC	CRIPT	CION	: SE	O ID	NO:	109:					
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	
45	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly	
			Glu 35					40					45				
		50	Thr				55					60					
50	65		Tyr			70					75					80	
			Asp		85	_				90		_	-		95		
55			Ile	100			_	_	105			-		110			
	val	гλε	Phe	GTU	атА	Asp	Thr	Leu	val	Asn	Arg	TTE	GTA	Leu	гÀв	GIA	

197

			115					120					125			
	Tle	Asp		Lvs	Glu	Asp	Glv		Tle	Len	G] v	His		Len	Glu	<b>ጥ</b> ህ ዮ
		130		Ly G	Q_Lu	****P	135	21044		DCu	017	140	272	204	U_ u	-7-
	Asn		Asn	Ser	His	Asn		Tvr	Ile	Met	Ala		Lvs	Gln	Lvs	Asn
5	145	•				150		•			155		_		•	160
	Gly	Ile	Lys	Val	Asn	Phe	Lys	Ile	Arg	His	Asn	Ile	Glu	Asp	Gly	Ser
	-		-		165		_		_	170				-	175	
	Val	Gln	Leu	Ala	qaA	His	Tyr	Gln	Gln	Asn	Thr	Pro	Ile	Gly	Asp	Gly
				180					185				•	190		
10	Pro	Val	Leu	Leu	Pro	qaA	Asn	His	Tyr	Leu	Ser	Thr	Gln	Ser	Ala	Leu
			195					200					205			
	Ser	Lys	Asp	Pro	Asn	Glu	Lys	Arg	Asp	His	Met	Val	Leu	Leu	Glu	Phe
		210					215	_			_	220	_	_	_	_
45		Thr	Ala	Ala	Gly		Thr	Leu	Gly	Met	_	Glu	Leu	Tyr	Lys	
15	225	•	•			230	<b>~</b> 1		<b>.</b>	•	235		14 - A	D	3	240
	GIĀ	ьeu	Arg	ser	Arg	AIA	GIR	Ala	ser		ser	Ala	Met	PLO	255	Pro
	ח ז ה	71-	ui e	Ton	245 Pro	Dhe	Dhe	77% 250	C1.	250	T10	602	7.20	פות		λla
	ATA	мта	пть	260	PIO	FIIC	FIIC	TYL	265	SEL	TTE	DET	Arg	270	Gru	ATA
20	Glu	Glu	нів		Lys	T.en	Δla	Glv		Δla	Δsn	Glv	Len		Len	T.eu
	014		275		270			280		*****	p	<b>U</b> -1	285			
	Ara	Gln		Leu	Arg	Ser	Leu		Glv	Tvr	Val	Leu		Leu	Val	His
	5	290	-1-				295	1	,	-1-		300				
	Asp	Val	Arg	Phe	His	His	Phe	Pro	Ile	Glu	Arq	Gln	Leu	Asn	Gly	Thr
25	305		_			310					315				-	320
	Tyr	Ala	Ile	Ala	Gly	Gly	Lys	Ala	His	Cys	Gly	Pro	Ala	Glu	Leu	Cys
					325					330					335	
	Glu	Phe	Tyr	Ser	Arg	qaA	Pro	qaA	Gly	Leu	Pro	Cys	Asn	Leu	Arg	Lys
				340					345					350		
30	Pro	Cys	Asn	Arg	Pro	Ser	Gly	Leu	Glu	Pro	Gln	Pro	_	Val	Phe	Asp
			355				<b>_</b>	360					365	_•	_	_
	Cys		Arg	Asp	Ala	Met		Arg	qaA	Tyr	Val		Gln	Thr	Trp	Lys
	<b>T</b>	370	<b>01</b>	<b>a</b> 1	B 1 -	<b>7</b>	375	<b>~1</b>	n1_	<b>71.</b>	<b>71</b> -	380	a1		<b>D</b>	<i>α</i> 1 =
35		GIU	GIY	GIU	Ala	леи 390	GIU	GIN	Ата	тте	395	ser	GIII	Ата	PIO	400
55	385	Glu	Taro	Len	Ile		Thr	Thr	አገລ	vi.		7~~	Mat	Dro	للحلولة	
	vai	GIU	шуъ	neu	405	ALG	1111	1111	MIA	410	GIU	Arg	MEC	FTO	415	+ Y -
	His	Ser	Ser	Len		Ara	Glu	Glu	Δla		Δτα	Lvs	Leu	Tvr		Gly
				420		5			425		5	7-		430		2
40	Ala	Gln	Thr	Asp	Gly	Lys	Phe	Leu		Arq	Pro	Arq	Lys	Glu	Gln	Gly
			435	_	_	-		440		_		_	445			-
	Thr	Tyr	Ala	Leu	Ser	Leu	Ile	Tyr	Gly	Lys	Thr	Val	Tyr	His	Tyr	Leu
		450					455					460				
	Ile	Ser	Gln	Asp	Lys	Ala	Gly	Lys	Tyr	Cys	Ile	Pro	Glu	Gly	Thr	ГÀЗ
45	465					470					475					480
	Phe	Asp	Thr	Leu		Gln	Leu	Val	Glu	_	Leu	Lys	Leu	Lys		Asp
		_		_	485	_	_			490	_	_	_	_	495	
	GIY	Leu	Ile		Cys	Leu	Lys	Glu		Cys	Pro	Asn	ser		Ala	Ser
EΛ				500	.1.		27	D	505	•	B		TT -	510	C	mb~
50	ASN	ALA		GIY	АТА	Ala	ATA		Thr	Leu	Pro	Ата	525	PIO	ser	Thr
	T.e.	Thr	515 Hie	Dro	Gln	Δνα	Δ۳α	520	Δer	ጥኤ፦	T.e.	Dan		Acn	Glv	Tyr
	LGU	530	1112	110		my	535	**G	rap	1111	neu	540	JUL	F	1	-1-
	Thr		Glu	Pro	Ala	Ara		Thr	Ser	Pro	Asp		Pro	Ara	Pro	Met
55	545				_ ~	550					555	4	_	,		560
		Met	Asp	Thr	Ser			Glu	Ser	Pro		Ser	Asp	Pro	Glu	Glu

198

```
565
                                     570
     Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Asp Asn Leu Leu Ile Ala
                       585
                                         590
     Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val Arg Gln Gly Val
5
                              600
     Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile Lys Val Leu Lys
              615
                                • 620
     Gln Gly Thr Glu Lys Ala Asp Thr Glu Glu Met Met Arg Glu Ala Gln
                       630
                                           635
10
     Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg Leu Ile Gly Val
                    645
                                      650
     Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met Ala Gly Gly Gly
                                   665
     Pro Leu His Lys Phe Leu Val Gly Lys Arg Glu Glu Ile Pro Val Ser
15
                    680
     Asn Val Ala Glu Leu Leu His Gln Val Ser Met Gly Met Lys Tyr Leu
                            695
     Glu Glu Lys Asn Phe Val His Arg Asp Leu Ala Ala Arg Asn Val Leu
                        710
                                           715
20
     Leu Val Asn Arg His Tyr Ala Lys Ile Ser Asp Phe Gly Leu Ser Lys
                    725
                                      730
     Ala Leu Gly Ala Asp Asp Ser Tyr Tyr Thr Ala Arg Ser Ala Gly Lys
                                  745
     Trp Pro Leu Lys Trp Tyr Ala Pro Glu Cys Ile Asn Phe Arg Lys Phe
25
                               760
     Ser Ser Arg Ser Asp Val Trp Ser Tyr Gly Val Thr Met Trp Glu Ala
                           775
                                              780
     Leu Ser Tyr Gly Gln Lys Pro Tyr Lys Lys Met Lys Gly Pro Glu Val
                       790
                                          795
30
     Met Ala Phe Ile Glu Gln Gly Lys Arg Met Glu Cys Pro Pro Glu Cys
                    805
                                       810
     Pro Pro Glu Leu Tyr Ala Leu Met Ser Asp Cys Trp Ile Tyr Lys Trp
                                   825
     Glu Asp Arg Pro Asp Phe Leu Thr Val Glu Gln Arg Met Arg Ala Cys
35
                  840
     Tyr Tyr Ser Leu Ala Ser Lys Val Glu Gly Pro Pro Gly Ser Thr Gln
     Lys Ala Glu Ala Ala Cys Ala
                        870
40
              (2) INFORMATION FOR SEQ ID NO:110:
           (i) SEQUENCE CHARACTERISTICS:
             (A) LENGTH: 2598 base pairs
45
             (B) TYPE: nucleic acid
             (C) STRANDEDNESS: single
             (D) TOPOLOGY: linear
           (ii) MOLECULE TYPE: cDNA
50
           (ix) FEATURE:
              (A) NAME/KEY: Coding Sequence
              (B) LOCATION: 1...2595
              (D) OTHER INFORMATION:
55
           (xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:
```

199

,	Met		CCC Pro	Ala				Phe				Ile		48
5	1			5				10				15		
ŭ			GCC Ala 20											96
10			CTG Leu		Cys									144
15			CAC His										_	192
20			ACC Thr									_		240
			TGC Cys											288
25			AAG Lys 100											336
30			GAC Asp											384
35			AAG Lys											432
40			CAG Gln											480
45			TAC Tyr											<b>528</b>
70			GGG Gly 180											576
50			GGC Gly				Ser				Lys			624
55		Tyr				Asp				Туг			CCC	672

200

																	•
					TTT												720
	225	GIÀ	Thr	гÀа	Phe	230	Thr	Leu	Trp	Gln		Val	Glu	Tyr	Leu	•	
5	223					230					235					240	
	CTG	AAG	GCG	GAC	GGG	CTC	ATC	TAC	TGC	CTG	AAG	GAG	GCC	TGC	CCC	AAC	768
	Leu	ГÀв	Ala	Asp	Gly	Leu	Ile	Tyr				Glu	Ala	Сув	Pro	Asn	
					245					250					255		
10	AGC	AGT	GCC	AGC	AAC	GCC	TCA	GGG	GCT	GCT	GCT	ccc	ACA	CTC	CCA	GCC	816
					Asn												010
				260					265					270			
	CNC	~~»	Ti C C	7 CC	TTG	n om	CI A III	ccm	asa.	1 C 1	<b>aa</b> 3	*	<b>a.</b> a.	3.00	ama	220	0.54
15					Leu												864
			275					280		•••	9	110	285		Dea	ADII	
									•								
					ACC												912
20	261	290	GTÅ	TÄT	Thr	PIO	295	PIO	AIA	Arg	116	300	ser	Pro	Asp	тÀа	
•												•••					
					CCC												960
	Pro 305	Arg	Pro	Met	Pro		Asp	Thr	Ser	Val	-	Glu	Ser	Pro	Tyr		
25	303		•			310					315					320	
	GAC	ĊCA	GAG	GAG	CTC	AAG	GAC	AAG	AAG	CTC	TTC	CTG	AAG	CGC	GAT	AAC	1008
	Asp	Pro	Glu	Glu	Leu	Lys	Asp	ГÀв	Lys	Leu	Phe	Leu	Lys	Arg	Asp	Asn	
					325					330					335		
30	CTC	CTC	ATA	GCT	GAC	ATT	GAA	CTT	GGC	TGC	GGC	AAC	ттт	GGC	TCA	GTG	1056
					Asp												
				340					345					350			
	CGC	CAG	GGC	GTG	TAC	CGC	ልጥር	ccc	מממ	מממ	CAG	ልጥሮ	GAC	GTG.	GCC	<b>አ</b> ሞሮ	1104
35					Tyr												1104
			355					360		_			365				
	770	OTTO	CTC	224	an a	000	» cc	ara.	220	002	ana	T 00	C3.3	a. a	» mai	N EFFC	7150
		_			CAG Gln												1152
40	4	370		-1-		1	375		-,-			380					
					ATC												1200
	385	GLU	Ата	GIII	Ile	390	UTR	GIII	теп	Asp	395	Pro	TYE	TTE	Val	400	
45																	
					TGC												1248
	Leu	Ile	GIY	Val	Cys 405	GIn	Ala	Glu	Ala	Leu 410	Met	Leu	Val	Met		Met	
					400	_				410					415		
50					CCG												1296
	Ala	Gly	Gly		Pro	Leu	His	Lys		Leu	Val	Gly	Lys		Glu	Glu	
				420					425					430			
	ATC	CCT	GTG	AGC	AAT	GTG	GCC	GAG	CTG	CTG	CAC	CAG	GTG	TCC	ATG	GGG	1344
55					Asn												
			435					440					445	•			

5												CGT Arg 460					1392
												AAG Lys					1440
10												TAC Tyr					1488
15	Ser	Ala	Gly	Lys 500	Trp	Pro	Leu	Lys	Trp 505	Tyr	Ala	CCC Pro	Glu	Cys 510	Ile	Asn	1536
20	Phe	Arg	<b>L</b> ув 515	Phe	Ser	Ser	Arg	Ser 520	Asp	Val	Trp	AGC Ser	Tyr 525	Gly	Val	Thr	1584
25	Met	Trp 530	Glu	Ala	Leu	Ser	Tyr 535	Gly	Gln	Lys	Pro	TAC Tyr 540	Lys	Lys	Met	Lys	1632
												AAG Lys					1680
30	_						_			_		ATG Met					1728
35	_				_							ACC Thr	_	_	_		1776
40		_							_			GTG Val	_	_			1824
45												TGG Trp 620					1872
	_											ACC Thr					1920
50												CAC His					1968
55										Tyr		AAG Lys				AAG Lys	2016

202

_		ATC Ile									2064
5		ACC Thr 690									2112
10		AAG Lys									2160
15		GAG Glu						•			2208
20		GAG Glu									2256
25		GGC Gly									2304
		TAC Tyr 770									2352
30		AAC Asn									2400
35		AGC Ser								_	2448
40		GGC Gly							_		2496
45		CTG Leu									2544
70		TTC Phe 850									2592
50	AAG Lys 865	TAA									2598

55 (2) INFORMATION FOR SEQ ID NO:111:

```
(i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 865 amino acids
              (B) TYPE: amino acid
              (C) STRANDEDNESS: single
5
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: protein
            (v) FRAGMENT TYPE: internal
10
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:
     Met Pro Asp Pro Ala Ala His Leu Pro Phe Phe Tyr Gly Ser Ile Ser
     Arg Ala Glu Ala Glu Glu His Leu Lys Leu Ala Gly Met Ala Asp Gly
15
                                      25
     Leu Phe Leu Leu Arg Gln Cys Leu Arg Ser Leu Gly Gly Tyr Val Leu
                                 40
      Ser Leu Val His Asp Val Arg Phe His His Phe Pro Ile Glu Arg Gln
                              55
20
     Leu Asn Gly Thr Tyr Ala Ile Ala Gly Gly Lys Ala His Cys Gly Pro
                         70
      Ala Glu Leu Cys Glu Phe Tyr Ser Arg Asp Pro Asp Gly Leu Pro Cys
                                         90 .
      Asn Leu Arg Lys Pro Cys Asn Arg Pro Ser Gly Leu Glu Pro Gln Pro
25
                                     105
     Gly Val Phe Asp Cys Leu Arg Asp Ala Met Val Arg Asp Tyr Val Arg
                                  120
      Gln Thr Trp Lys Leu Glu Gly Glu Ala Leu Glu Gln Ala Ile Ile Ser
                              135
                                                 140
30
      Gln Ala Pro Gln Val Glu Lys Leu Ile Ala Thr Thr Ala His Glu Arg
                         150
                                            155
      Met Pro Trp Tyr His Ser Ser Leu Thr Arg Glu Glu Ala Glu Arg Lys
                     165
                                         170
     Leu Tyr Ser Gly Ala Gln Thr Asp Gly Lys Phe Leu Leu Arg Pro Arg
35
                 180
                                     185
     Lys Glu Gln Gly Thr Tyr Ala Leu Ser Leu Ile Tyr Gly Lys Thr Val
                                 200
                                                     205
      Tyr His Tyr Leu Ile Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro
                             215
                                      . 220
40
      Glu Gly Thr Lys Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys
                         230
                                             235
      Leu Lys Ala Asp Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn
                                          250
      Ser Ser Ala Ser Asn Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala
45
                                      265
      His Pro Ser Thr Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn
                                  280
      Ser Asp Gly Tyr Thr Pro Glu Pro Ala Arg Ile Thr Ser Pro Asp Lys
                              295
50
      Pro Arg Pro Met Pro Met Asp Thr Ser Val Tyr Glu Ser Pro Tyr Ser
                                              315
      Asp Pro Glu Glu Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Asp Asn
                                          330
      Leu Leu Ile Ala Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val
55
                                      345
      Arg Gln Gly Val Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile
```

			355					360					365			
	Lys	Val 370	Leu	Lys	Gln	Gly	Thr 375	Glu	ГÀЗ	Ala	Asp	Thr 380	Glu	Glu	Met	Met
5	Arg 385	Glu	Ala	Gln	Ile	Met 390	His	Gln	Leu	Ąsp	Asn 395	Pro	Tyr	Ile	Val	Arg 400
	Leu	Ile	Gly	Val	Cys 405	Gln	Ala	Glu	Ala	Leu 410	Met	Leu	Val	Met	Glu 415	Met
	Ala	Gly	Gly	Gly 420	Pro	Leu	His	Lys	Phe 425	Leu	Val	Gly	Lys	Arg 430	Glu	Glu
10	Ile	Pro	Val 435	Ser	Asn	Val	Ala	Glu 440	Leu	Leu	His	Gln	Val 445	Ser	Met	Gly
	Met	Lys 450	Tyr	Leu	Glu	Glu	Lys 455	Asn	Phe	Val	His	Arg 460	Авр	Leu	Ala	Ala
15	Arg 465	Asn	Val	Leu	Leu	Val 470	Asn	Arg	His	Tyr	Ala 475	Lys	Ile	Ser	Asp	Phe 480
	Gly	Leu	Ser	ГÀЗ	Ala 485	Leu	Gly	Ala	Asp	Asp 490	Ser	Tyr	Tyr	Thr	Ala 495	Arg
	Ser	Ala	Gly	Lys 500	Trp	Pro	Leu	Lys	Trp 505	Tyr	Ala	Pro	Glu	Cys 510	Ile	Asn
20	Phe	Arg	Lys 515	Phe	Ser	Ser	Arg	Ser 520	Asp	Val	Trp	Ser	Tyr 525	Gly	Val	Thr
	Met	Trp 530	Glu	Ala	Leu	Ser	Tyr 535	Gly	Gln	Lys	Pro	Tyr 540	ГÀЗ	ГÀа	Met	Lys
25	Gly 545	Pro	Glu	Val	Met	Ala 550	Phe	Ile	Glu	Gln	Gly 555	ГÀЗ	Arg	Met	Glu	Cys 560
	Pro	Pro	Glu	Cys	Pro 565	Pro	Glu	Leu	Tyr	Ala 570	Leu	Met	Ser	Asp	Cys 575	Trp
	Ile	Tyr	Lys	Trp 580	Glu	Asp	Arg	Pro	Asp 585	Phe	Leu	Thr	Val	Glu 590	Gln	Arg
30	Met	Arg	Ala 595	Cys	Tyr	Tyr	Ser	Leu 600	Ala	Ser	Lys	Val	Glu 605	Gly	Pro	Pro
	Gly	Ser 610	Thr	Gln	Lys	Ala	Glu 615	Ala	Ala	Cys	Ala	Trp 620	Asp	Pro	Pro	Val
35	Ala 625	Thr	Met	Val	Ser	Lys 630	Gly	Glu	Glu	Leu	Phe 635	Thr	Gly	Va1	Val	Pro 640
	Ile	Leu	Val	Glu	Leu 645	Asp	Gly	Asp	Val	Asn 650	Gly	His	ГÀв	Phe	Ser 655	Val
	Ser	Gly	Glu	Gly 660	Glu	Gly	qaA	Ala	Thr 665	Tyr	Gly	Lys	Leu	Thr 670	Leu	Lys
40			675	Thr			_	680				_	685			
	Thr	Thr 690	Leu	Thr	Tyr	Gly	Val 695	Gln	Cys	Phe	Ser	Arg 700	Tyr	Pro	Asp	His
45	Met 705	Lys	Gln	His	Asp	Phe 710	Phe	Lys	Ser	Ala	Met 715	Pro	Glu	Gly	Tyr	Va]
	Gln	Glu	Arg	Thr	Ile 725	Phe	Phe	ГÀв	Asp	Asp 730	Gly	Asn	Tyr	ГÀв	Thr 735	Arc
	Ala	Glu	Val	Lys 740	Phe	Glu	Gly	Asp	Thr 745		Val	Asn	Arg	Ile 750	Glu	Let
50	Lys	Gly	Ile 755	Asp	Phe	Lys	Glu	Asp 760	Gly	Asn	Ile	Leu	Gly 765	His	Lys	Let
	Glu	Tyr 770		Tyr	Asn	Ser	His 775		Val	Tyr	Ile	Met 780		Asp	Lys	Gli
55	Lys 785		Gly	Ile	Lys	Val 790	Asn	Phe	Lys	Ile	Arg 795		Asn	Ile	Glu	Asp 800
	Glv	Ser	Val	Gln	Leu	Ala	Asp	His	Tvr	Gln	Gln	Asn	Thr	Pro	Ile	Gly

										205	•						
					805					810					815		
	Asp	Gly	Pro		Leu	Leu	Pro	qaA		His	Tyr	Leu	Ser		Gln	Ser	
	Ala	Leu	Ser	820 Lvs	Asp	Pro	Asn	Glu	825 Lvs	Ara	Asp	His	Met	830 Val	Leu	Lev	
5			835	-,-				840	-1-	•••			845		201	200	
	Glu	Phe 850	Val	Thr	Ala	Ala	Gly 855	Ile	Thr	Leu	Gly	Met 860	Asp	Glu	Leu	Tyr	
	Lys																
10	865																
			(2)	INI	ORMA	TION	FOF	SEC	Q ID	NO: 1	12:						
15		i)	(B) (C)	LENC TYPE STR	NCE ( TH: 3: nu NDEI DLOGY	1635 Iclei NESS	bas c ac : si	se pa cid ingle	airs								
20		Ι.	Li) N Lx) I			TYPE	E: cI	ANC									·
25		()	(B)	LOC	ME/KE CATIO HER I	N: 1	LI	L632 CON:	 -		NO: 1	112:					
			AAC Asn														48
30	1				5	_,_	•		_,_	10	<b></b> ,	-	<b>0-</b> <i>y</i>		15		
			TAC														96
			•	20		_		•	25					30			
35	N N C	3 A B	ATC	999	ama	<b>a</b>	3 CM	a.a	3 CID	a. c	aam	ama	999	3 CM	3 CIM	000	244
			Ile														144
٠	-	-	35	_		-		40			-		45				
40	איזיכי	CGA	GAG	ልጥሮ	ጥርጥ	СТС	سس	AAG	GAG	ىلىرلىپ	አልሮ	ሮልጥ	لبالبيلة	יייממ	ΔΨΨ	GTC	192
. •		_	Glu			_	_							_			
		50					55					60					
	DAG	СТС	CTG	GAT	GTC	ידידמ	CAC	ACA	GAA	ידממ	ΔΔΔ	CTC	TAC	CTG	GTT	վական	240
45			Leu														
	65					70					75					80	
	GAA	TTT	CTG	CAC	CAA	GAT	CTC	AAG	AAA	TTC	ATG	GAT	GCC	TCT	GCT	CTC	288
			Leu														
50					85					90					95		
	ACT	GGC	ATT	CCT	CTT	CCC	CTC	ATC	AAG	AGC	TAT	CTG	TTC	CAG	CTG	CTC	336
			Ile														
55				100					105					110			
JJ	CAG	GGC	CTA	GCT	TTC	TGC	CAT	TCT	CAT	CGG	GTC	CTC	CAC	CGA	GAC	CTT	384
																	2

	Gln	Gly	Leu 115	Ala	Phe	Cys	His	Ser 120	His	Arg	Val	Leu	His 125	Arg	Asp	Leu		
5				AAT Asn													432	
10				CTA Leu													480	
45				GTG Val												_	528	
15				TAT Tyr 180													576	
20				ATG Met													624	
25				CTC Leu													672	
30				CCA Pro													720	
05				GCC Ala												_	768	
35				CGG Arg 260													816	
40				TCG Ser													864	
45				CCA Pro									Pro				912	
50				AGC Ser								Gly				ATC Ile 320	960	
						Gly					His					TCC	1008	
55	GGC	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	CTG	ACC	CTG	AAG	TTC	1056	206

207

									`									
	Gly	Glu	Gly	Glu 340	Gly	Asp	Ala	Thr	Tyr 345	Gly	ГÀЗ	Leu	Thr	Leu 350	ГÀЗ	Phe		
5												CCC Pro			_			1104
10												TAC Tyr 380						1152
45												GAA Glu				_		1200
15												TAC Tyr				_		1248
20												CGC Arg						1296
25												GGG Gly						1344
30												GCC Ala 460						1392
												AAC Asn						1440
35												ACC Thr		_	_			1488
40										Tyr		AGC Ser						1536
45				Asp					Arg					Leu		GAG Glu		1584
50			Thr					Thr				GAC Asp 540	Glu			AAG Lys	Т	1633
	AA																	1635
			,_															

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:

55

208

(A) LENGTH: 544 amino acids

- (B) TYPE: amino acid(C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

10 Met Glu Asn Phe Gln Lys Val Glu Lys Ile Gly Glu Gly Thr Tyr Gly Val Val Tyr Lys Ala Arg Asn Lys Leu Thr Gly Glu Val Val Ala Leu Lys Lys Ile Arg Leu Asp Thr Glu Thr Glu Gly Val Pro Ser Thr Ala 15 Ile Arg Glu Ile Ser Leu Leu Lys Glu Leu Asn His Pro Asn Ile Val 55 Lys Leu Leu Asp Val Ile His Thr Glu Asn Lys Leu Tyr Leu Val Phe 20 70 Glu Phe Leu His Gln Asp Leu Lys Lys Phe Met Asp Ala Ser Ala Leu 90 Thr Gly Ile Pro Leu Pro Leu Ile Lys Ser Tyr Leu Phe Gln Leu Leu 105 25 Gln Gly Leu Ala Phe Cys His Ser His Arg Val Leu His Arg Asp Leu 120 Lys Pro Gln Asn Leu Leu Ile Asn Thr Glu Gly Ala Ile Lys Leu Ala 1.35 Asp Phe Gly Leu Ala Arg Ala Phe Gly Val Pro Val Arg Thr Tyr Thr 30 155 150 His Glu Val Val Thr Leu Trp Tyr Arg Ala Pro Glu Ile Leu Leu Gly 165 170 Ser Lys Tyr Tyr Ser Thr Ala Val Asp Ile Trp Ser Leu Gly Cys Ile 185 35 Phe Ala Glu Met Val Thr Arg Arg Ala Leu Phe Pro Gly Asp Ser Glu 200 Ile Asp Gln Leu Phe Arg Ile Phe Arg Thr Leu Gly Thr Pro Asp Glu 220 215 Val Val Trp Pro Gly Val Thr Ser Met Pro Asp Tyr Lys Pro Ser Phe 40 230 235 Pro Lys Trp Ala Arg Gln Asp Phe Ser Lys Val Val Pro Pro Leu Asp 250 Glu Asp Gly Arg Ser Leu Leu Ser Gln Met Leu His Tyr Asp Pro Asn 265 Lys Arg Ile Ser Ala Lys Ala Ala Leu Ala His Pro Phe Phe Gln Asp 45 280 Val Thr Lys Pro Val Pro His Leu Arg Leu Trp Asp Pro Pro Val Ala 300 295 Thr Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile 50 310 315 Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser 330 Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe 345 Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr 55

	Thr	Leu 370	Thr	Tyr	Gly	Val	Gln 375	Cys	Phe	Ser	Arg	Tyr 380	Pro	Asp	His	Met	
	Lys 385	Gln	His	Asp	Phe	Phe 390	Lys	Ser	Ala	Met	Pro 395	Glu	Gly	Tyr	Val	Gln 400	
5	_	Arg	Thr	Ile	Phe 405	Phe	Lys	Asp	Asp	Gly 410		Tyr	Lys	Thr	Arg 415		
	Glu	Val	Lys	Phe 420		Gly	Asp	Thr	Leu 425		Asn	Arg	Ile	Glu 430		Lys	
40	Gly	Ile	-		Lys	Glu	Asp			Ile	Leu	Gly		-	Leu	Glu	
10	Tyr		435 Tyr	Asn	ser	His		440 Val	Tyr	Ile	Met		445 Asp	ГЛВ	Gln	Lys	
	Nen	450	aſT	Lve	Va 1	Asn	455 Dhe	T.va	Tle	Δνα	ui e	460	Tle	Glu	Agn	Glv	
	465	GIY	116	пуь	Val	470	FIIC	шув	116	ALG	475	ASII	110	GIU	мар	480	
15		Val	Gln	Leu	Ala 485	Asp	His	Tyr	Gln	Gln 490		Thr	Pro	Ile	Gly 495	Asp	
	Gly	Pro	Val	Leu 500		Pro	Asp	Asn	His 505		Leu	Ser	Thr	Gln 510		Ala	
20	Leu	Ser	<b>L</b> ув 515		Pro	Asn	Glu	Lys 520		Asp	His	Met	Val 525		Leu	Glu	
20	Phe	Val		Ala	Ala	Gly	Ile		Leu	Glv	Met	asa		Leu	Tyr	Lvs	
		530					535					540			•	•	
25			(2)	INI	ORM	ATIOI	1 FOI	R SE	Q ID	NO:	114:						
25		7.	i) er	ייייייייייייייייייייייייייייייייייייי	ורדי (	CHAR	ומיזים	סדפיתי	TCC.								
		\-	-			163											
						ucle		-			•						
						ONES			е								
30			(D)	TOPO	)LOG	Y: 1:	inea	r									
				MOLEC		TYPI	E: cl	AND	•								
		١.	L.X./ .	PAL	JRE;												
35						EY: (		_	eque	nce							
						ON:											
		(3	ki) S	SEQUI	ENCE	DES	CRIP	TION	: SE	Q ID	NO:	114:					
40																	4.5
						GAG Glu											48
	1	val	261	пув	5	Giu	GIU	neu	PILE	10	GIY	Val	Vai	FIG	15	neu	
45						GAC											96
	Val	Glu	Leu	_	Gly	Asp	Val	Asn	_	His	Lys	Phe	Ser		Ser	Gly	
				20					25					30			
						GCC											144
50	Glu	GTÀ	G1u 35	GTÀ	Asp	Ala	Thr	Tyr 40	ĠΙÅ	гÀв	ьeu	rnr	Leu 45	ràe	rne	тте	
						CTG											192
55	Сув	Thr	Thr	Gly	ьув	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr	

					:	210					
								CCC Pro			240
5								GGC Gly			288
10								AAG Lys			336
15								ATC Ile			384
20	 							CAC His 140			432
								GAC Asp	_		480
25								ATC Ile			528
30								CCC Pro			576
35								ACC Thr			624
40								GTC Val 220			672
40								GAG Glu			720
45							Gln	AAG Lys			768
50								AGA Arg			816
55		Val			Ile			GAC Asp	Glu	GAG Glu	864

						 211					
	GTG Val 290										912
5	CAT His										960
10	CTC Leu										1008
15	GAT Asp										1056
00	CTG Leu										1104
20	CTC Leu 370										1152
25	 GCC Ala	 									1200
30	GTT Val										1248
35	GAA Glu										1296
40	AGC Ser								_		1344
40	CCT Pro 450									_	1392
45	GGG										1440
50	TAC Tyr			Phe			Arg				1488
55	GTA Val		Leu			Arg			Gln	ATG Met	1536

212

									- 2	212								
		CAC His																1584
5		CCT Pro 530														CTC :	r	1633
	GA																	1635
10			(2)	TNE	ODM	\TT^\	t EOY	CEC	. TD	NO . 1	16.							
			(2)	INF	ORM	11101	v ror	COE	) ID	MO: 1	. 15:							
15		(i	(A) (B) (C)	LENG TYPE STRA	ETH: E: an	THARM 544 mino ONESS Y: 1:	amin ació 3: si	no ac i ingle	cids		•							
20						TYPI TYPE												
		(х	ci) S	EQUI	ENCE	DES	CRIP'	rion	: SE(	OI O	NO : 1	115:					•	
25	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu		
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly		
•	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile		
30	Сув	Thr 50		Gly	гàа	Leu	Pro 55		Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr		
	Leu 65	Thr	Tyr	Gly	Val	Gln 70		Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80		
35		His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu		
	Arg	Thr	Ile	Phe 100		Lys	qeA	Авр	Gly 105		Tyr	Lys	Thr	Arg 110	Ala	Glu		
	Val	Lys	Phe 115		Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	ГÀЗ	Gly		
40	Ile	Asp 130		Lys	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr		
	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val		Ile	Met	Ala 155	qaA	Lys	Gln	ГÀв	Asn 160		
45		Ile	Lys	Val	Asn 165		Lys	Ile	Arg	His 170	Asn	Ile	Glu	Ąsp	Gly 175	Ser		
	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185		Thr	Pro	Ile	Gly		Gly		
	Pro	Val	Leu 195		Pro	Asp	Asn	His	Tyr		Ser	Thr	Gln 205		Ala	Leu		
50	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg		His	Met	Val 220	Leu		Glu	Phe		
		Thr		Ala	Gly		Thr		Gly	Met		Glu		Tyr	ГЛЗ	Ser		
	225 Gly		Arg	Ser	-			Glu	. Asn				Val	Glu		240 Ile		
55	Gly	Glu	Gly	Thr	245 Tyr		. Val	. Val	. Tyr	250 Lys		Arg	Asn	Lys	255 Let	Thr		

213

				260		_	_	_	265	_				270			
			275					280				Asp	285				
5	Gly	Val 290	Pro	Ser	Thr	Ala	Ile 295	Arg	Glu	Ile	Ser	Leu 300	Leu	Lys	Glu	Leu	
		His	Pro	Asn	Ile		Lys	Leu	Leu	Asp		Ile	His	Thr	Glu		
	305	T	m	T	17- 1	310	<b>43</b>	Dl	<b>-</b>	**	315	<b>-</b>	•	•	<b>-</b>	320	
	ъуs	ьеи	TYL	ьeu	325	rne	GIU	Pne	Leu	330	GIN	Asp	Leu	гув	шув 335	Pne	
10	Met	Asp	Ala	Ser 340	Ala	Leu	Thr	Gly	Ile 345	Pro	Leu	Pro	Leu	Ile 350	Lys	Ser	
	Tyr	Leu	Phe 355	Gln	Leu	Leu	Gln	Gly 360	Leu	Ala	Phe	Сла	His 365	Ser	His	Arg	
15	Val		His	Arg	Asp	Leu	Lys 375		Gln	Asn	Leu	Leu		Asn	Thr	Glu	
15	Gly	370 Ala	Ile	Lys	Leu	Ala		Phe	Gly	Leu	Ala	380 Arg	Ala	Phe	Gly	Val	
	385					390	_				395					400	
	Pro	Val	Arg	Thr	Tyr 405	Thr	His	Glu	Val	Val 410	Thr	Leu	Trp	Tyr	Arg 415	Ala	
20	Pro	Glu	Ile	Leu 420	Leu	Gly	Ser	Lys	Tyr 425	Tyr	Ser	Thr	Ala	Val 430	qaA	Ile	
	Trp	Ser	Leu 435		Cys	Ile	Phe	Ala 440		Met	Val	Thr	Arg		Ala	Leu	
0.5	Phe			Asp	Ser	Glu			Gln	Leu	Phe	Arg		Phe	Arg	Thr	
25	T	450	ш	D	n	<b>a</b> 3	455	17_ 7		D	a1	460	m\	0	<b>M</b> = F	D	
	465	GTĀ	THE	PIO	Asp	470	vaı	vai	TIP	Pro	475	Val	Thr	ser	met	480	
	Asp	Tyr	Lys	Pro	Ser 485	Phe	Pro	Lys	Trp	Ala 490	Arg	Gln	Asp	Phe	Ser 495	ГÅв	
30	Val	Val	Pro	Pro 500		Asp	Glu	Asp	Gly 505		Ser	Leu	Leu	Ser 510		Met	
	Leu	His	_		Pro	Asn	Lys	_		Ser	Ala	Lys			Leu	Ala	
	His	Pro	515 Phe	Phe	Gln	Asp	Val	520 Thr	Lys	Pro	Val	Pro	525 His	Leu	Arg	Leu	
35		530					535					540					
			(2)	INI	FORM	ATIOI	V FO	R SE	Q ID	NO:	116:						
		(:	i) SI	EQUE	ICE (	CHAR	ACTE	RIST:	ICS:								
40						253					,						
						ucle:											
						DNES: Y: 1:			9								
		•	(D)	TOP	JLOG.	1: 1.	inea.	L									
45				MOLE FEAT		TYP	E: c	AMC									
		ν.	LA,	CEAL	JKE:												
						EY: (		_	eque:	nce							
50						ON: INFO											
		(:	xi) :	SEQU	ENCE	DES	CRIP	TION	: SE	Q ID	NO:	116:					
	אַתיני	GTC	≱ניר	- אינו	GGC	GΣα	GZG	ריידי		ארר	GGG	GMG	מיים	כייי	ልጥሮ	CTG	48
55					Gly										Ile	Leu	•-
	1				5					10					15		

214

5		GAG Glu								96
Ü		GGC Gly								144
10		ACC Thr 50								192
15		ACC Thr								240
20		CAC His								288
25		ACC Thr								336
		AAG Lys	_	 _						384
30	_	GAC Asp 130								432
35		TAC Tyr								480
40		ATC Ile								528
45		CAG Gln								576
		GTG Val								624
50		AAA Lys 210								672
55		ACC Thr								720

5	CTC Leu											768
J	AGT Ser											816
10	AGC Ser											864
15	TCC Ser 290											912
20	GGG											960
25	GAG Glu											1008
	GAC Asp											1056
30	ACT Thr											1104
35	ACG Thr 370											1152
40	AGC Ser											1200
45	CCC Pro											1248
40	ATG Met											1296
50	AGC Ser		Thr			His			Gly			1344
55		Ser			Tyr			Tyr		_	ACG Thr	1392

5		GTG Val								1440
		CAG Gln								1488
10		AGT Ser								1536
15	_	CAG Gln								1584
20		TTT Phe 530								1632
25		GGG Gly								1680
		CCT Pro								1728
30		GCC Ala								1776
35		GTC Val								1824
40		GTC Val 610								1872
45		TCT Ser								1920
		ACC Thr								1968
50		TGG Trp								2016
55		CCT Pro								2064

										•	•						
		AGT Ser 690															2112
5																	
	ATC	GGC	CGC	ACA	GGC	ACC	ATC	ATT	GTC	ATC	GAC	ATG	CTC	ATG	GAG	AAC	2160
	Ile	Gly	Arg	Thr	Gly	Thr	Ile	Ile	Val	Ile	Asp	Met	Leu	Met	Glu	Asn	
	705	-	_			710					715					720	
10	ATC	TCC	ACC	AAG	GGC	CTG	GAC	TGT	GAC	ATT	GAC	ATC	CAG	AAG	ACC	ATC	2208
	Ile	Ser	Thr	Lys	Gly	Leu	Asp	Сув	Asp	Ile	Asp	Ile	${\tt Gln}$	Lys	Thr	Ile	
					725					730					735		
																	•
		ATG															2256
15	Gln	Met	Val		Ala	Gln	Arg	Ser	_		Val	Gln	Thr		Ala	Gln	
				740					745	•				750			
				3.00	m = ~	ama	~~~	3 M/C	~~~	~~~	mma	7. CTV	~~~	300	3 CM	***	2204
		AAG															2304
20	туг	Lys		TTE	TÄT	Val	MIG	760	Ald	GIII	Pile	TIE	765	1111	TILL	цуs	
20			755					700					705				
	AAG	AAG	ריידיני	GZG	GTC	כיוויני	CAG	TCG	CAG	DAG	GGC	CAG	GAG	TCG	GAG	TAC	2352
		Lys															
	-7-	770					775		<del></del>	1-	3	780				-2-	
25																	
	GGG	AAC	ATC	ACC	TAT	CCC	CCA	GCC	ATG	AAG	AAT	GCC	CAT	GCC	AAG	GCC	2400
	Gly	Asn	Ile	Thr	Tyr	Pro	Pro	Ala	Met	Lys	Asn	Ala	His	Ala	Lys	Ala	
	785					790					795					800	
30		CGC															2448
	Ser	Arg	Thr	Ser		Lys	Hls	Lys	Glu	_	vai	Tyr	GIU	ASN		HIS	
					805					810					815		
	א ריידי	AAG	אאר	מממ	AGG	GAG	GAG	מממ	GTG	ממ	AAG	CAG	CGG	TCA	GCA	GAC	2496
35		Lys				_	_					_				_	
•••		_, _		820	_			-, -	825	-,-			3	830		**- <b>F</b>	
	AAG	GAG	AAG	AGC	AAG	GGT	TCC	CTC	AAG	AGG	AAG	TGA					2532
	Lys	Glu	Lys	Ser	Lys	Gly	Ser	Leu	Lys	Arg	Lys						
40			835					840									
			(2	) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	117:						
4E		,	2 ، ۵			~*** T	3 CITIES		T 00								
45		(		EQUE													
				LEN TYP					Clas								
				STR													
				TOP					.C								
50			(2)		0,000			-									
		(	ii}	MOLE	CULE	TYP	E: r	rote	in		•						
				RAGM													
		•															
		(	xi)	SEQU	ENCE	DES	CRIE	TION	: SE	Q II	NO:	117:					
55																	
	Met	. Val	. Ser	Lys	Gly	Glu	ı Glu	Lev	Phe	Thr	Gly	/ Val	. Val	Pro	Ile	e Leu	
																	_

									•	C 10						
	1				5					10					15	
	Val	Glu	Leu	Asp 20	Gly	qaA	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
5	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Сув	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	B0 Lys
10			qaA		85					90		-	_		95	
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu
15		-	Phe 115		_			120					125			
		130	Phe	-			135					140				
20	145	-	Asn			150					155		-			160
20	-		Lys		165		_		_	170				_	175	
•	Val			180	-		-		185					190	_	
25			Leu 195			_		200	-				205			
		210	Asp Ala				215					220				
30	225		Arg		_	230			_		235					240
30	-		Gly		245					250	_	_			255	
			Phe	260					265					270		
35	•		275 Val			-		280	_	=			285			
		290	Asp				295					300				
40	305	_	Leu		_	310		-	_	_	315	_				320
					325	_	_			330		_			335	
				340					345					350		Ala
45			355					360	-				365			Arg
	-	370					375					380				Asp
50	385					390					395					400
50			-		405					410					415	
			_	420					425					430		Phe
55	_		435					440					445			Glu
	GLU	Ala	ser	GLY	АТа	rne	val	ıyr	ьeu	Arg	GID	PTO	тут	TAL	ATA	Thr

219

		450					455					460				
	Arg 465		Asn	Ala	Ala	Asp 470		Glu	Asn	Arg	.Val		Glu	Leu	Asn	Lys 480
5		Gln	Glu	Ser	Glu 485		Thr	Ala	ГÀв	Ala 490		Phe	Trp	Glu	Glu 495	
-	Glu	Ser	Leu	Gln 500		Gln	Glu	Val	Lys 505		Leu	His	Gln	Arg 510		Glu
	Gly	Gln	Arg 515		Glu	Asn	ГÀЗ	Gly 520		Asn	Arg	Tyr	Lys 525		Ile	Leu
10	Pro	Phe 530	Asp	His	Ser	Arg	Val 535		Leu	Gln	Gly	Arg 540	Asp	Ser	Asn	Ile
	Pro 545	Gly	Ser	Asp	Tyr	Ile 550	Asn	Ala	Asn	Tyr	Ile 555	Lys	Asn	Gln	Leu	Leu 560
15	Gly	Pro	Asp	Glu	Asn 565	Ala	Lys	Thr	Tyr	Ile 570	Ala	Ser	Gln	Gly	Cys 575	Leu
	Glu	Ala	Thr	Val 580	Asn	ĄsĄ	Phe	Trp	Gln 585	Met	Ala	Trp	Gln	Glu 590	Asn	Ser
	Arg	Val	Ile 595	Val	Met	Thr	Thr	Arg 600	Glu	Val	Glu	ГÀв	Gly 605	Arg	Asn	Lys
20	_	610	Pro	-	_		615		_			620		-	_	
	625		Val			630					635					640
25			Leu		645				_	650	_	_			655	
			His	660					665	•			_	670		
20			Gly 675					680					685			
30		690	Leu				695					700	_			_
	705		Arg		_	710					715					720
35			Thr		725			_	_	730				-	735	
			Val	740			_		745					750		
40			Phe 755 Leu					760					765			
70		770	Ile				775			_	_	780				_
	785		Thr		_	790				_	795					800
45			Asn		805	=		=		810		=	•		815	
			Lys	820					825			GIII	<b></b> 9	830	1124	1101
50	-,,		835		273	<u></u> y		840	-73	****9	פעם					
			(2	) IN	FORM	ATIO	N FO	R SE	o in	NO:	118:					

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2562 base pairs
  - (B) TYPE: nucleic acid

55

(C) STRANDEDNESS: single

									:	220								
			(D)	TOPO	) POG 7	7: li	near	<b>:</b>										
				OLEC		TYPE	E: cI	ANC									,	
5		\-						_										
			(B)	LOC	ATIC	)N: 1	١2	2559	equer	ıce								
4.0				OTI														
10		()	ci) S	EQUE	ENCE	DESC	RIPT	: NOI	: SEQ	DID	NO:	118:						
				CGT Arg	_												48	
15	1			J	5	•			J	10			4		15			
				CTC													96	
	GLu	Thr	Leu	Leu 20	гÀг	GIÀ	Arg	GIA	Val 25	His	GTA	Ser	Phe	Leu 30	Ala	Arg		
20	CCC	AGT	CGC	AAG	AAC	CAG	GGT	GAC	TTC	TCG	CTC	TCC	GTC	AGG	GTG	GGG	144	
	Pro	Ser	Arg 35	Lys	Asn	Gln	Gly	Asp 40	Phe	Ser	Leu	Ser	Val 45	Arg	Val	Gly		
	GAT	CAG	GTG	ACC	CAT	ATT	CGG	ATC	CAG	AAC	TCA	GGG	GAT	TTC	TAT	GAC	192	
25	Asp	Gln 50	Val	Thr	His	Ile	Arg 55	Ile	Gln	Asn	Ser	Gly 60	Asp	Phe	Tyr	Asp		
				GGG													240	
30	ьец 65	тут	GIY	Gly	GIU	ьуs 70	Pne	Ala	THE	ьeu	75	GIU	Leu	vaı	GIU	80		
				CAG													288	
	Tyr	Thr	Gin	Gln	85	GIÀ	vaı	Leu	GIn	Asp 90	Arg	Asp	СТУ	rnr	95	TTE		
35	CAC	CTC	AAG	TAC	CCG	CTG	AAC	TGC	TCC	GAT	CCC	ACT	AGT	GAG	AGG	TGG	336	
	His	Leu	Lys	Tyr 100	Pro	Leu	Asn	Cys	Ser 105	Asp	Pro	Thr	Ser	Glu 110	Arg	Trp		
40				CAC													384	
	Tyr	His	115	His	Met	Ser	GIÀ	120	Gln	Ala	Glu	Thr	Leu 125	Leu	GIn	Ala		
45				CCC													432	
45	гуs	130	GLu	Pro	Trp	Thr	135	Leu	Val	Arg	GIu	5er 140	Leu	ser	GIN	Pro		
				GTG													480	
50	145	wab	FIIG	Val	neu	150	ActT	neu	oer	чар	155		пåя	WIG	GTÅ	160		
				CTC													528	
	gry	ser	PTO	Leu	Arg 165	val	Thr	Hls	īīe	Lys 170	val	мес	cys	GIU	175	стА		
55	CGC	TAC	ACA	GTG	GGT	GGT	TTG	GAG	ACC	TTC	GAC	AGC	CTC	ACG	GAC	CTG	576	
			_															220

SUBSTITUTE SHEET (RULE 26)

	Arg	Tyr	Thr	Val 180	Gly	Gly	Leu	Glu	Thr 185	Phe	Asp	Ser	Leu	Thr 190	Asp	Leu	
5		GAG Glu															624
10		TAC Tyr 210															672
15		GAG Glu															720
13		GCC Ala															768
20		GTG Val															816
25		GGC Gly															864
30		ATC Ile 290															912
		GCC Ala															960
35		ACC Thr															1008
40		TGG Trp															1056
45		CGA Arg															1104
50		GTG Val 370															1152
FF		GAG Glu															1200
55	CCG	CTG	GAC	AAT	GGA	GAC	CTG	ATT	CGG	GAG	ATC	TGG	CAT	TAC	CAG	TAC	1248

		_	_	_			_		_			_		_		_		
	Pro	Leu	Asp	Asn	Gly 405	qaA	Leu	Ile	Arg	Glu 410	Ile	Trp	His	Tyr	Gln 415	Tyr		
_			TGG														1296	
5	Leu	Ser	Trp	Pro 420	Asp	His	Gly	Val	Pro 425	Ser	Glu	Pro	Gly	Gly 430	Val	Leu		
			CTG Leu														1344	
10	201		435					440	5				445					
	ദദദ	רככ	ATC	ATC	GTG	CAC	TGC	AGC	GCC	GGC	ATC	GGC	CGC	ACA	GGC	ACC	1392	
			Ile															
15		450					455					460						
10			GTC														1440	
	Ile 465	Ile	Val	Ile	Asp	Met 470	Leu	Met	Glu	Asn	Ile	Ser	Thr	Lys	Gly	Leu 480		
										•								
20			GAC Asp														1488	
	мар	Cyb	nop		485		0.111	_,_	~***	490	0111				495			
	CGC	ጥሮር	GGC	ΔΤС	GTG	CAG	<b>V</b> CG	GAG	GCG	CAG	ፐልሮ	DAG	TTC	ATC	TAC	GTG	1536	
25			Gly															
				500					505					510				
			GCC														1584	
30	Ala	Ile	Ala 515	Gln	Phe	Ile	Glu	Thr 520	Thr	ГЛЯ	ГÀЗ	Lys	Leu 525	Glu	Val	Leu		
00																		
			CAG Gln														1632	
		530		-1-	1		535			1-	2	540			•			
35	CCA	GCC	ATG	AAG	ААТ	GCC	CAT	GCC	AAG	GCC	TCC	CGC	ACC	TCG	TCC	AAA	1680	
			Met								Ser					Lys		
	545					550					555					560		
40			GAG														1728	
	His	Lys	Glu	Asp	Val 565	Tyr	Glu	Asn	Leu	His 570	,	Lys	Asn	Lys	Arg 575	Glu		
45			GTG Val													GGT Gly	1776	
	<b></b>	_,_		580	_,_	0		552	585		-,-		-,-	590	-, -			
	TCC	СТС	DAG	AGG	AAG	CGA	ATT	CTG	CAG	TCG	ACG	GTA	CCG	CGG	GCC	CGG	1824	
								Leu	Gln				Pro	Arg		Arg		
50			595					600					605					
																ACC	1872	
	Asp	Pro 610		Val	Ala	Thr	Met 615		Ser	rys	Gly	Glu 620		Leu	Phe	Thr		
55						_				_				_				
	GGG	GTG	GTG	CCC	ATC	CTG	GTC	GAG	CTG	GAC	GGC	GAC	: GTA	AAC	GGC	CAC	1920	222

	Gly 625	Val	Val	Pro	Ile	Leu 630	Val	Glu	Leu	Авр	Gly 635	Asp	Val	Asn	Gly	His 640	
5		TTC Phe															1968
10		ACC Thr															2016
		ACC Thr															2064
15		CCC Pro 690															2112
20		GGC Gly															2160
25		AAG Lys															2208
30		ATC Ile															2256
		CAC His															2304
35	_	GAC Asp 770					_									_	2352
40		ATC Ile															2400
45		CCC Pro															2448
50		ACC Thr															2496
		GTC Val							Ala								2544
55	GAC	GAG	CTG	TAC	AAG	TAA					•						2562 22

224

Asp Glu Leu Tyr Lys 850

```
5
               (2) INFORMATION FOR SEO ID NO:119:
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 853 amino acids
              (B) TYPE: amino acid
10
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: protein
            (v) FRAGMENT TYPE: internal
15
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:
     Met Leu Ser Arg Gly Trp Phe His Arg Asp Leu Ser Gly Leu Asp Ala
20
     Glu Thr Leu Leu Lys Gly Arg Gly Val His Gly Ser Phe Leu Ala Arg
                                     25
     Pro Ser Arg Lys Asn Gln Gly Asp Phe Ser Leu Ser Val Arg Val Gly
                                 40
     Asp Gln Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp
25
     Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr
     Tyr Thr Gln Gln Gln Gly Val Leu Gln Asp Arg Asp Gly Thr Ile Ile
                                         90
30
     His Leu Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp
                                     105
     Tyr His Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala
                                 120
     Lys Gly Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro
35
                            135
                                                 140
     Gly Asp Phe Val Leu Ser Val Leu Ser Asp Gln Pro Lys Ala Gly Pro
                         150
                                             155
     Gly Ser Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly
                     165
                                         170
40
     Arg Tyr Thr Val Gly Gly Leu Glu Thr Phe Asp Ser Leu Thr Asp Leu
                                     185
     Val Glu His Phe Lys Lys Thr Gly Ile Glu Glu Ala Ser Gly Ala Phe
                                         -
                                  200
      Val Tyr Leu Arg Gln Pro Tyr Tyr Ala Thr Arg Val Asn Ala Ala Asp
45
                              215
                                                  220
      Ile Glu Asn Arg Val Leu Glu Leu Asn Lys Lys Gln Glu Ser Glu Asp
                          230
                                              235
      Thr Ala Lys Ala Gly Phe Trp Glu Glu Phe Glu Ser Leu Gln Lys Gln
                                          250
50
      Glu Val Lys Asn Leu His Gln Arg Leu Glu Gly Gln Arg Pro Glu Asn
                                      265
      Lys Gly Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Ser Arg
                                  280
      Val Ile Leu Gln Gly Arg Asp Ser Asn Ile Pro Gly Ser Asp Tyr Ile
55
                              295
                                                  300
```

224

Asn Ala Asn Tyr Ile Lys Asn Gln Leu Leu Gly Pro Asp Glu Asn Ala

	305					310					315					320
					325				_	330			Thr		335	Asp
5				340					345				Ile	350		
			355					360					Pro 365	_	_	
		370					375		_			380	Val			
10	385					390					395		Leu			400
					405				_	410			His	-	415	_
15			_	420	_		-		425				Gly -	430		
			435	_				440	-				Leu 445			
00	_	450					455			_		460	Arg		_	
20	11e 465	11e	vaı	TIE	Asp	мес 470	Leu	Met	GIu	Asn	11e 475	ser	Thr	ГÀВ	GIY	Leu 480
		-	_		485			_		490			Val	_	495	
25				500					505				Phe	510		
			515					520		_	_	_	Leu 525			
		530					535					540	Ile			
30	545			_		550					555		Thr			560
					565					570			Asn		575	
35				580					585				Lys	590		
			595					600					Pro 605			
		610					615			_	_	620	Glu			
40	625					630				_	635	_	Val			640
	_				645	_		_		650	-		Thr	_	655	_
45				660					665				Pro	670		
			675					680	_	_			Сув 685			
	_	690					695		_			700				
50	Glu 705	Gly	Tyr	Val	Gln	Glu 710	_	Thr	Ile	Phe	Phe 715	_	Asp	Asp	Gly	720
	Tyr	Lys	Thr	Arg	Ala 725	Glu	Val	Lys	Phe	Glu 730	_	Asp	Thr	Leu	Val 735	Asr
55	Arg	Ile	Glu	Leu 740	_	Gly	Ile	Asp	Phe 745	-	Glu	Asp	Gly	Asn 750		Let
	Glv	His	Lvs	Leu	Glu	Tyr	Asn	Tvr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met

			755					760					765					
	Ala	Asp 770	Lys	Gln	Lys	Asn	Gly 775	Ile	Lys	Val	Asn	Phe 780	Lys	Ile	Arg	His		
E		Ile	Glu	Asp	Gly		Val	Gln	Leu	Ala	_	His	Tyr	Gln	Gln			
5	785 Thr	Pro	Ile	Gly		790 Gly	Pro	Val	Leu		795 Pro	Asp	Asn	His		800 Leu		
	Ser	Thr	Gln		805 Ala	Leu	Ser	ГЛа		810 Pro	Asn	Glu	Lys		815 Asp	His		
10	Met	Val	Leu	820 Leu	Glu	Phe	Val	Thr	825 Ala	Δla	Glv	Ile	ጥh ጕ	830 Len	Glv	Met		
		Glu	835					840			017		845	Dou	U.J	1100		
	р	850		-,-	2,0													
15			(2)	INE	ORM	ATION	FOF	SEÇ	Q ID	NO:	L20:							
		i)	i) SE															
				TYPE				se pa	alrs									
20				STRA				ingle :	•									
		13	Li) N															
			ix) i			1111	s: CI	,										•
25			(A)	NAN	Œ/KE	3Y: (	odir	ng Se	equer	ıce								
			(B)	LO	CATIO	ON: 1	L2	2991	•									
			(11)	OTI	iek .	LNFOR	CMAIL	LON:										
30		()	ci) S	EQUI	ENCE	DESC	RIPT	NOI?	: SE(	) ID	NO:	120:						
												GTG					48	
	Met 1	vaı	ser	гув	GIA GIA	GIu	GIU	ьeu	Pne	Thr 10	GIA	Val	Val	Pro	11e 15	Leu		
35	ርሞር	GNG	כיזיכי	GNC	aac	GAC	CUTA	አአሮ	aac	CNC	770	TTC	אפפ	CTYC.	maa	ccc	96	
												Phe					90	
				20					25					30				
40												ACC					144	
	GII	GIA	35	GIY	Asp	Ala	Thr	Tyr 40	GIA	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile		
•	<b>יי</b> יפר	אכיכי	אממ	aaa	አስር	CTC	aaa	ana	acc	maa	ccc	ACC	CEC	CTTCT	N.C.C	N.C.C.	100	
45												Thr					192	
		50					55					60						
												CCC					240	
50	ьеи 65	Inr	туг	GTÀ	vaı	70	CÀB	Pne	ser	Arg	1yr 75	Pro	Asp	H18	мес	80 гуз		
	CAG	CAC	GAC	TTC	TTC	DAA	TCC	GCC	ATG	ccc	GAA	GGC	TAC	GTC	CAG	GAG	288	
					Phe					Pro		Gly			Gln			
55					85					90					95			
	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	336	
																		226

227

	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	ГÀЗ	Thr	Arg 110	Ala	Glu	
5		AAG Lys															384
10		GAC Asp 130															432
15		TAC Tyr															480
13		ATC Ile															528
20		CAG Gln														_	576
25		GTG Val															624
30		AAA Lys 210															672
		ACC Thr															720
35		CTC Leu															768
40		GGG Gly															816
45		GGC Gly														GAA Glu	864
50		GAT Asp 290															912
		Asn					Cys					Ile				TTG Leu 320	960
55	AAC	CAT	GCC	AAT	GTT	GTA	AAG	GCC	TGT	GAT	GTT	CCT	GAA	. GAA	TTG	AAT	1008

4	Asn	His	Ala	Asn	Val 325	Val	Lys	Ala	Сув	Asp 330	Val	Pro	Glu	Glu	Leu 335	Asn		
5				CAT					Leu					Cys			1056	
	GGA	GAT	CTC	340 CGA	AAG	CTG	CTC	AAC	345 AAA	CCA	GAA	AAT	TGT	350 TGT	GGA	CTT	1104	
10	Gly	Asp	Leu 355	Arg	Lys	Leu	Leu	Asn 360	ГÀЗ	Pro	Glu	Asn	Суя 365	Cys	Gly	Leu		
		Glu		CAG Gln			Ser					Ile					1152	
15		370					375					380						
				CAT His													1200	
	385					390				-	395			_		400		
20				CTT Leu													1248	
	71311		vul		405	пор	142	CLI	Cly	410		110	1115	БуБ	415			
25				TAT													1296	
25	Asp	neu	GIÀ	Tyr 420	AIA	пув	Asp	vai	425	GII	GIĀ	ser	neu	430	TOF	ser		
				ACA Thr													1344	
30			435				_	440					445			-		
				GCC Ala													1392	
35		450					455	-2-	<b>x</b>			460						
				GCT Ala													1440	
	465	CID	110	712.0	dry	470	my	110	riic	Deu	475	1115	neu	<b>J111</b>	110	480		
40				GAG Glu													1488	
	****	пр	1140	<b>3.u</b>	485		<b>1</b> 175	ny o	БуБ	490	FIO	шуъ	cys	116	495	Ata		
45				ATG Met													1536	
	-			500		•			505		•			510				
				CTT Leu													1584	
50	-		515		4			520					525			<del>-</del>		
				TTG Leu													1632	
55		530	1 3 to G	u		1	535	110	Litt	0111	v. a	540	OLY	-10	Val	TOP		
00	CTT	ACT	TTG	AAG	CAG	CCA	AGA	TGT	TTT	GTA	TTA	ATG	GAT	CAC	ATT	TTG	1680	228
																		220

229

	Leu 545	Thr	Leu	Lys	Gln	Pro 550	Arg	Cys	Phe	Val	Leu 555	Met	Asp	His	Ile	Leu 560	,
5					GTA Val 565												1728
10					CCA Pro												1776
15					ACT Thr												1824
15					TCT Ser												1872
20					AGA Arg							_					1920
25					GTA Val 645												1968
30					TAT Tyr												2016
25	_	_			AAA Lys	_								_		_	2064
35					TAT Tyr												2112
40					AGA Arg												2160
45					TCA Ser 725												2208
50					CTT Leu												2256
																GAA Glu	2304
55	AAG	GCC	ATC	CAC	TAT	GCT	GAG	GTT	GGT	GTC	ATT	GGA	TAC	CTG	GAG	GAT	2352 2

230

	Lys	Ala 770	Ile	His	Tyr	Ala	Glu 775	Val	Gly	Val	Ile	Gly 780	Tyr	Leu	Glu	Asp	
5		ATT Ile															2400
10		GGA Gly															2448
15		GAT Asp															2496
,		GAC Asp		_													2544
20		GAC Asp 850															2592
25		TGT Cys															2640
30		AGT Ser															2688
35		AGG Arg															2736
		TCT Ser															2784
40		CAG Gln 930			_												2832
45		CTG Leu															2880
50		ATA Ile															2928
55		GAG Glu															2976
	AGT	TGG	TTA	ACA	GAA	TGA											2994 2 <b>3</b> 0

•

231

Ser Trp Leu Thr Glu 995

```
5 (2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 997 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
```

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(D) TOPOLOGY: linear

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
20		Glu		20					25					30	Ser	_
		Gly	35					40					45			
25	Сув	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
	65	Thr				70					75					80
		His			85					90					95	
30		Thr		100					105					110		
		ГÀв	115					120					125			
35		Asp 130					135					140				
	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	ГÀв	Gln	Lys	Asn 160
	Gly	Ile	Lys	Val	Asn 165	Phe	Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser
40	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly
	Pro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200	Tyr	Leu	Ser	Thr	Gln 205	Ser	Ala	Leu
45	Ser	Lys 210	qaA	Pro	Asn	Glu	Ьув 215	Arg	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe
	Val 225	Thr	Ala	Ala	Gly	Ile 230	Thr	Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	ГÀЗ	Ser 240
	Gly	Leu	Arg	Ser	Arg 245	Ala	Gln	Ala	Ser	Asn 250	Ser	Thr	Met	Glu	Arg 255	
50	Pro	Gly	Leu	Arg 260	Pro	Gly	Ala	Gly	Gly 265	Pro	Trp	Glu	Met	Arg 270	Glu	Arg
	Leu	Gly	Thr 275	Gly	Gly	Phe	Gly	Asn 280	Val	Сув	Leu	Tyr	Gln 285	His	Arg	Glu
55	Leu	Asp 290	Leu	Lys	Ile	Ala	Ile 295	Lys	Ser	Сув	Arg	Leu 300	Glu	Leu	Ser	Thr
	ГÀв	Asn	Arg	Glu	Arg	Trp	Cys	His	Glu	Ile	Gln	Ile	Met	Lys	Lys	Leu

	305					310					315					320
	Asn	His	Ala	Asn	Val 325	Val	ГÀв	Ala	Cys	Asp 330	Val	Pro	Glu	Glu	Leu 335	Asn
5				His 340					345					350		
			355	Arg				360					365	_		
	ГÀЗ	Glu 370	Ser	Gln	Ile	Leu	Ser 375	Leu	Leu	Ser	Asp	Ile 380	Gly	Ser	Gly	Ile
10	Arg 385	Tyr	Leu	His	Glu	Asn 390	Lys	Ile	Ile	His	Arg 395	Asp	Leu	Lys	Pro	Glu 400
	Asn	Ile	Val	Leu	Gln 405	Asp	Val	Gly	Gly	Lys 410	Ile	Ile	His	Lys	Ile 415	Ile
15	Asp	Leu	Gly	Tyr 420	Ala	Lys	Asp	Val	Asp 425	Gln	Gly	Ser	Leu	Cys 430	Thr	Ser
	Phe	Val	Gly 435	Thr	Leu	Gln	Tyr	Leu 440	Ala	Pro	Glu	Leu	Phe 445	Glu	Asn	Lys
	Pro	Tyr 450	Thr	Ala	Thr	Val	Asp 455	Tyr	Trp	Ser	Phe	Gly 460	Thr	Met	Val	Phe
20	465	_		Ala	_	470					475					480
				Glu	485				_	490		_	_		495	
25	Cys	Glu	Glu	Met 500	Ser	Gly	Glu	Val	Arg 505	Phe	Ser	Ser	His	Leu 510	Pro	Gln
			515	Leu				520					525			
	Gln	Leu 530	Met	Leu	Asn	Trp	Asp 535	Pro	Gln	Gln	Arg	Gly 540	Gly	Pro	Val	Asp
30	545			ГÀЗ		550		_			555		_			560
				Ile	565					570				_	575	
35				Leu 580					<b>5</b> 85					590		
			595	Glu				600					605			
		610		Ile			615			_		620				
40	625			Val		630				_	635		_			640
				Thr	645			_		650			_		655	
45				Asn 660					665					670		
			675	Arg				680					685			
	Leu	Lуs	Glu	Asp	Tyr	Ser	Arg 695	Leu	Phe	Gln	Gly	Gln 700	Arg	Ala	Ala	Met
50	705			Leu		710					715					720
				Ala	725				-	730	_				735	
55	_			Gln 740					745	-				750		_
	Glv	Tla	Ser	Ser	Glu	Tayo	Mot	T.OU	Taze	Δla	J. J.	Tave	Glu	Met	Gin	Gli

			755					760					765				
	Lys	Ala 770	Ile	His	Tyr	Ala	Glu 775		Gly	Val	Ile	Gly 780		Leu	Glu	Ąsp	
5	Gln 785	Ile	Met	Ser	Leu	His 790	Ala	Glu	Ile	Met	Gly 795	Leu	Gln	Lys	Ser	Pro 800	
	Tyr	Gly	Arg	Arg	Gln 805	Gly	qaA	Leu	Met	Glu 810	Ser	Leu	Glu	Gln	Arg 815	Ala	
	Ile	Asp	Leu	Tyr 820	Lys	Gln	Leu	Lys	His 825		Pro	Ser	Asp	His 830		Tyr	
10	Ser	qaA	Ser 835	Thr	Glu	Met	Val	Lys 840	Ile	Ile	Val	His	Thr 845	Val	Gln	Ser	
	Gln	Asp 850	Arg	Val	Leu	Lys	Glu 855	Leu	Phe	Gly	His	Leu 860	Ser	Lys	Leu	Leu	
15	Gly 865	Cys	Lys	Gln	Lys	Ile 870	Ile	Asp	Leu	Leu	Pro 875	Lys	Val	Glu	Val	Ala 880	
٠	Leu	Ser	Asn	Ile	Lys 885	Glu	Ala	Asp	Asn	Thr 890	Val	Met	Phe	Met	Gln 895		
	Lys	Arg	Gln	Lys 900		Ile	Trp	His	Leu 905		Lys	Ile	Ala	Cys 910		Gln	
20	Ser	Ser	Ala 915		Ser	Leu	Val	Gly 920		Ser	Leu	Glu	Gly 925		Val	Thr	
	Pro	Gln 930		Ser	Ala	Trp	Leu 935		Pro	Thr	Ser	Ala 940		His	Asp	His	
		Leu	Ser	Cys	Val			Pro	Gln	Asp		Glu	Thr	Ser	Ala		
25	945	T10	C1.,	C1.,	λan	950	A an	Cira	T 011	<i>α</i> 1	955	T 0	Com	Mlb se	T10	960	
	MEC	Ile	GIU	GIU	965	пеп	ASII	Сув	Ten	970	птв	Leu	per	THE	975	TTE	
	His	Glu	Ala	Asn 980		Glu	Gln	Gly	Asn 985		Met	Met	Asn	Leu 990		Trp	
30	Ser	Trp	Leu 995		Glu												
•			(2)	IN	ORM	TION	1 FOI	R SE(	Q ID	NO:	122:						
35		13	i) SI														
		(-	(A)	LENG	TH:	299	L bas	se pa									
					i nu ANDEI				<b>e</b> .		٠						
40			(D)	TOP	DLOG	7: 1:	inear	r									
40			ii) N ix) I			TYPI	E: cI	ANC									
			· (A)	NAI	ME/KI	3Y: (	Codin	ng Se	eguei	ace							
45			(B)	LO	CATIO	on:	12	2988	-								
		(:	ki) S	SEQU	ENCE	DES	CRIP	rion	: SE	Q ID	NO:	122:					
50	ATG	GAG	CGG	CCC	CCG	GGG	CTG	CGG	CCG	GGC	GCG	GGC	GGG	CCC	TGG	GAG	48
		Glu															
		CGG															96
55	Met	Arg	Glu	Arg 20	Leu	GLY	Thr	Gly	Gly 25	Phe	Gly	Asn	Val	Cys	Leu	Tyr	

234

5			GAA Glu											144
3			ACC Thr											192
10			TTG Leu											240
15			AAT Asn											288
20			GGA Gly 100	_								_		336
25		_	CTT Leu		_	_							_	384
	_	_	ATT Ile			_			_	_				432
30			GAA Glu											480
35		_	ATT Ile				_				_	_		528
40			TCT Ser 180					 						576
45			AAG Lys											624
			TTT Phe											672
50			TTT Phe											720
55			GCA Ala		Glu			 Glu					Ser	768

	CAT	TTA	CCT	CAA	CCA	AAT	AGC	CTT	TGT	AGT	TTA	ATA	GTA	GAA	ccc	ATG	816
5				Gln 260					265					270			
	GAA Glu	AAC Asn	TGG Trp 275	Leu	CAG Gln	TTG Leu	ATG Met	TTG Leu 280	AAT Asn	TGG Trp	GAC Asp	CCT Pro	CAG Gln 285	CAG Gln	AGA Arg	GGA Gly	864
10	GGA Gly	CCT Pro 290	GTT Val	GAC Asp	CTT	ACT Thr	TTG Leu 295	AAG Lys	CAG Gln	CCA Pro	AGA Arg	TGT Cys 300	TTT Phe	GTA Val	TTA Leu	ATG Met	912
15	GAT Asp 305	CAC His	ATT Ile	TTG Leu	AAT Asn	TTG Leu 310	AAG Lys	ATA Ile	GTA Val	CAC His	ATC Ile 315	CTA Leu	AAT Asn	ATG Met	ACT Thr	TCT Ser 320	960
20	GCA Ala	AAG Lys	ATA Ile	ATT Ile	TCT Ser 325	TTT Phe	CTG Leu	TTA Leu	CCA Pro	CCT Pro 330	GAT Asp	GAA Glu	AGT Ser	CTT Leu	CAT His 335	TCA Ser	1008
25	CTA Leu	CAG Gln	TCT Ser	CGT Arg 340	ATT Ile	GAG Glu	CGT Arg	GAA Glu	ACT Thr 345	GGA Gly	ATA Ile	TAA Asn	ACT Thr	GGT Gly 350	TCT Ser	CAA Gln	1056
	GAA Glu	CTT Leu	CTT Leu 355	TCA Ser	GAG Glu	ACA Thr	GGA Gly	ATT Ile 360	TCT Ser	CTG Leu	GAT Asp	CCT Pro	CGG Arg 365	AAA Lys	CCA Pro	GCC Ala	1104
30	TCT Ser	CAA Gln 370	TGT Cys	GTT Val	CTA Leu	GAT Asp	GGA Gly 375	GTT Val	AGA Arg	GGC Gly	TGT Cys	GAT Asp 380	AGC Ser	TAT Tyr	ATG Met	GTT Val	1152
35	TAT Tyr 385	TTG Leu	TTT Phe	GAT Asp	TA TA	AGT Ser 390	AAA Lys	ACT Thr	GTA Val	TAT Tyr	GAA Glu 395	GGG Gly	CCA Pro	TTT Phe	GCT Ala	TCC Ser 400	1200
40	AGA Arg	AGT Ser	TTA Leu	TCT Ser	GAT Asp 405	TGT Cys	GTA Val	AAT Asn	TAT Tyr	ATT Ile 410	GTA Val	CAG Gln	GAC Asp	AGC Ser	AAA Lys 415	ATA Ile	1248
45	CAG Gln	CTT Leu	CCA Pro	ATT Ile 420	ATA Ile	CAG Gln	CTG Leu	CGT Arg	AAA Lys 425	GTG Val	TGG Trp	GCT Ala	GAA Glu	GCA Ala 430	GTG Val	CAC His	1296
	TAT Tyr	GTG Val	TCT Ser 435	GGA Gly	CTA Leu	AAA Lys	GAA Glu	GAC Asp 440	TAT Tyr	AGC Ser	AGG Arg	CTC Leu	TTT Phe 445	CAG Gln	GGA Gly	CAA Gln	1344
50	AGG Arg	GCA Ala 450	GCA Ala	ATG Met	TTA Leu	AGT Ser	CTT Leu 455	CTT Leu	AGA Arg	TAT Tyr	AAT Asn	GCT Ala 460	AAC Asn	TTA Leu	ACA Thr	AAA Lys	1392
55	ATG Met 465	AAG Lys	AAC Asn	ACT Thr	TTG Leu	ATC Ile 470	TCA Ser	GCA Ala	TCA Ser	CAA Gln	CAA Gln 475	CTG Leu	AAA Lys	GCT Ala	AAA Lys	TTG Leu 480	1440

236

5		TTT Phe									1488
	_	ATG Met	_		_						1536
10		ATG Met									1584
15		CTG Leu 530									1632
20		AAG Lys									1680
25		CAG Gln									1728
20		CAC His									1776
30		GTG Val									1824
35		AAG Lys 610									1872
40		GAA Glu									1920
45		ATG Met									1968
		TGT Cys									2016
50		GCA Ala									2064
55		CAT His 690				Сув	 	 	Gln		2112

		TCA Ser															2160
5																	
		ACT															2208
	Ser	Thr	Ile	Ile		Glu	Ala	Asn	Glu		Gln	Gly	Asn	Ser		Met	
					725					730					735		
10	3 3 63	~~~	~~~	maa	3.00	maa	mm-										
10		CTT															2256
	MBII	Leu	Asp	740	Ser	ттр	Leu	Thr		Trp	Vai	Pro	Arg		Arg	Asp	
				740					745					750			
	CCA	CCG	GTC	GCC	ACC	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	יייי	ACC	GGG	2304
15		Pro															2501
			755					760	-,	1			765			<b>4</b> -1	
	GTG	GTG	CCC	ATC	CTG	GTC	GAG	CTG	GAC	GGC	GAC	GTA	AAC	GGC	CAC	AAG	2352
	Val	Val	Pro	Ile	Leu	Val	Glu	Leu	Asp	Gly	Asp	Val	Asn	Gly	His	Lys	
20		770					775			-	_	780		_		-	
		AGC															2400
		Ser	Val	Ser	Gly		Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	
0.5	785					790					795					800	
25	3.00																
		CTG															2448
	THE	Leu	гÃв	Pne		Сув	unr	unr	СТА		Leu	Pro	vaı	Pro	_	Pro	
					805					810					815		
30	ACC	CTC	GTG	ACC	ACC	СТС	ACC	<sub>ሞል</sub> ሮ	GGC	ата	CVG	TCC	שישיכי	AGC	CGC	ጥልሮ	2496
		Leu															2130
				820				-1-	825			-1-		830	5	-1-	
	CCC	GAC	CAC	ATG	AAG	CAG	CAC	GAC	TTC	TTC	AAG	TCC	GCC	ATG	CCC	GAA	2544
35	Pro	Asp	His	Met	Lys	Gln	His	Asp	Phe	Phe	Lys	Ser	Ala	Met	Pro	Glu	
			835					840					845				
		TAC															2592
40	GIA	Tyr	Val	Gln	Glu	Arg		Ile	Phe	Phe	Lys	_	qaA	Gly	Asn	Tyr	
40		850					855				•	860					
	AAG	ACC	CGC	GCC	GNG	GTG.	አለር	THE	G N G	ccc	CNC	700	CTC.	OTO.	224	ccc	2640
		Thr															2040
	865	1111		ALU	Olu	870	פעם	FIIC	GIU	Giy	875	1111	пеп	Val	WOII	880	
45											0,5					000	
	ATC	GAG	CTG	AAG	GGC	ATC	GAC	TTC	AAG	ĠAG	GAC	GGC	AAC	ATC	CTG	GGG	2688
	-	Glu															
				-	885		_		-	890	-	-			895	•	
														•			
50	CAC	AAG	CTG	GAG	TAC	AAC	TAC	AAC	AGC	CAC	AAC	GTC	TAT	ATC	ATG	GCC	2736
	His	Lys	Leu	Glu	Tyr	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	
				900					905					910			
	<b>a-</b> -		<b>~~</b> -			~~~		•		:							
55		AAG															2784
ູບວ	Asp	Lys	915	nys	ASN	GTA	TTG		val	Asn	rne	гÀа		Arg	HIS	ASN	
			213					920					925				

ATC GAG GAC GGC AGC GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC I Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn ' 930 935 940 5 CCC ATC GGC GAC GGC CCC GTG CTG CCC GAC AAC CAC TAC CTG	ACC 2832
	Ihr
	AGC 2880
Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu	
945 950 955	960
10 ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC	
10 ACC CAG TCC GCC CTG AGC AAA GAC CCC AAC GAG AAG CGC GAT CAC.  Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His 1	
965 970 975	
•	
GTC CTG CTG GAG TTC GTG ACC GCC GCC GGG ATC ACT CTC GGC ATG	
15 Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met . 980 985 990	Asp
300 303	
GAG CTG TAC AAG TAA	2991
Glu Leu Tyr Lys	
20 995	
(2) INFORMATION FOR SEQ ID NO:123:	
25 (i) SEQUENCE CHARACTERISTICS:	
(A) LENGTH: 996 amino acids	
(B) TYPE: amino acid	
(C) STRANDEDNESS: single	
(D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: protein	
(v) FRAGMENT TYPE: internal	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:	
Met Glu Arg Pro Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp	Glu
1 5 10 15	
Met Arg Glu Arg Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu	Tyr
20 25 30 40 Gln His Arg Glu Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg	ໂຂນ
is orn are indicate not tab act the received for the	
35 40 45	
	Ile
35 40 45 Glu Leu Ser Thr Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln 50 55 60	
35 40 45 Glu Leu Ser Thr Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln 50 55 60 Met Lys Lys Leu Asn His Ala Asn Val Val Lys Ala Cys Asp Val	Pro
35 40 45 Glu Leu Ser Thr Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln 50 55 60	Pro 80
45 Glu Leu Ser Thr Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln 50 55 60 Met Lys Lys Leu Asn His Ala Asn Val Val Lys Ala Cys Asp Val 45 65 70 75	Pro 80
Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   S	Pro 80 Glu
Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   S	Pro 80 Glu Asn
Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   S	Pro 80 Glu Asn
Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second Second	Pro 80 Glu Asn Ile
Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   S	Pro 80 Glu Asn Ile Asp
Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   Second   S	Pro 80 Glu Asn Ile Asp

					165					170					175	
	Leu	Cys	Thr	Ser 180	Phe	Val	Gly	Thr	Leu 185	Gln	Tyr	Leu	Ala	Pro 190	Glu	Leu
5			Asn 195					200					205			
		210	Val				215		-	_	_	220				
	225		Pro			230			-		235	_	_	_		240
10			Phe		245					250					255	
			Pro	260					265					270		
15			Trp 275					280		-	_		285			
		290					295				•	300				
20	305		Ile			310					315					320
20			Ile Ser		325					330					335	
			Leu	340					345	. "				350		
25			355 Cys					360			-		365	_		
		370	Phe				375					380				
30	385		Leu			390				_	395	_				400
	_		Pro		405				_	410			_		415	
			Ser	420					425		_			430		
35			435 Ala					440			_		445			
		450	Asn				455			_		460				
40	465		Phe			470					475					480
			Thr		485					490			_		495	
			Glu	500					505					510		
45	•		515 Glu					520					525			
		530	Ser				535					540				
50	545 Glu		Arg	Ala	Ile	550 Asp	Leu	Tyr	Lys	Gln	555 Leu	Lys	His	Arg	Pro	560 Ser
	Asp	His	Ser	Tyr	565 Ser	Asp	Ser	Thr	Glu	570 Met	Val	Lys	Ile	Ile	575 Val	His
	Thr	Val	Gln	580 Ser	Gln	Asp	Arg	Val	585 Leu	Lув	Glu	Leu	Phe	590 Gly	His	Leu
55	<b>9</b> 0~	Late	595 Lev	T.A.1	G) w	Cve	Luc	600	T 140	Tle	Tle	λαν	605	T.em	Dro	Tare

240

		610					615					620				
	Val	Glu	Val	Ala	Leu	Ser	Asn	Ile	Lys	Glu	Ala	Asp	Asn	Thr	Val	Met
	625					630					635					640
	Phe	Met	Gln	Gly	Lys	Arg	Gln	Lys	Glu	Ile	Trp	His	Leu	Leu	Lys	Ile
5					645					650	•				655	
	Ala	Cys	Thr	Gln	Ser	Ser	Ala	Arg	Ser	Leu	Val	Gly	Ser	Ser	Leu	Glu
				660					665					670		
	Gly	Ala	Val	Thr	Pro	Gln	Thr	Ser	Ala	Trp	Leu	Pro	Pro	Thr	Ser	Ala
			675					680		-			685			
10	Glu	His	Asp	His	Ser	Leu	Ser	Cys	Val	Val	Thr	Pro	Gln	Авр	Gly	Glu
		690					695	-				700				
	Thr	Ser	Ala	Gln	Met	Ile	Glu	Glu	Asn	Leu	Asn	Cys	Leu	Gly	His	Leu
	705					710					715	-		_		720
	Ser	Thr	Ile	Ile	His	Glu	Ala	Asn	Glu	Glu	Gln	Gly	Asn	Ser	Met	Met
15					725					730		_			735	
	Asn	Leu	qaA	Trp	Ser	Trp	Leu	Thr	Glu	Trp	Val	Pro	Arg	Ala	Arg	Авр
			-	740		-			745	-			_	750	-	-
	Pro	Pro	Val	Ala	Thr	Met	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly
			755					760	•	_			765			•
20	Val	Val	Pro	Ile	Leu	Val	Glu	Leu	Asp	Gly	Asp	Val	Asn	Gly	His	Lys
		770					775		_	_	_	780		_		_
	Phe	Ser	Val	Ser	Gly	Glu	Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu
	785				-	790	-			-	795		-	_	-	800
	Thr	Leu	Lys	Phe	Ile	Cys	Thr	Thr	Gly	Lys	Leu	Pro	Val	Pro	Trp	Pro
25			_		805	-			_	810					815	
	Thr	Leu	Val	Thr	Thr	Leu	Thr	Tyr	Gly	Val	Gln	Cys	Phe	Ser	Arg	Tyr
				820					825					830		
	Pro	Asp	His	Met	Lys	Gln	His	Asp	Phe	Phe	Lys	Ser	Ala	Met	Pro	Glu
			835					840					845			
30	Gly	Tyr	Val	Gln	$\operatorname{Glu}$	Arg	Thr	Ile	Phe	Phe	Lys	Asp	Asp	Gly	Asn	Tyr
		850					855					860				
	Lys	Thr	Arg	Ala	Glu	Val	Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg
	865					870					875					880
	Ile	Glu	Leu	Lys	Gly	Ile	Asp	Phe	Lys	Glu	Asp	Gly	Asn	Ile	Leu	Gly
35					885					890					895	
	His	Lys	Leu	Glu	Tyr	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala
				900					905					910		
	Asp	Lys	Gln	Lys	Asn	Gly	Ile	Lys	Val	Asn	Phe	Lys	Ile	Arg	His	Asn
			915					920					925			
40	Ile	Glu	Asp	Gly	Ser	Val	Gln	Leu	Ala	Asp	His	Tyr	Gln	Gln	Asn	Thr
		930			,		935					940				
	Pro	Ile	Gly	Asp	Gly	Pro	Val	Leu	Leu	Pro	Asp	Asn	His	Tyr	Leu	
	945					950					955					960
	Thr	Gln	Ser	Ala		Ser	Lys	Asp	Pro	Asn	Glu	Lys	Arg	Asp		Met
45					965					970					975	
	Val	Leu	Leu		Phe	Val	Thr	Ala		_	Ile	Thr	Leu		Met	Asp
				980					985					990		
	Glu	Leu	_	Lys												
			995													
50																

(2) INFORMATION FOR SEQ ID NO:124:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1908 base pairs
  - (B) TYPE: nucleic acid

55

(C) STRANDEDNESS: single

241

(ii) MOLECULE TYPE: cDNA

(D) TOPOLOGY: linear

(ix) FEATURE:

5

(A) NAME/KEY: Coding Sequence (B) LOCATION: 1...1905

(D) OTHER INFORMATION:

			,,,	, 01		11110	M. DAT	ION:									
10		(	xi)	SEQU	ENCE	DES	CRIP	TION	: SE	Q ID	NO:	124:					
15	ATG Met 1	GTG Val	AGC Ser	AAG Lys	GGC Gly 5	GAG Glu	GAG Glu	CTG Leu	TTC Phe	ACC Thr 10	GGG	GTG Val	GTG Val	CCC Pro	ATC Ile 15	CTG Leu	48
	GTC Val	GAG Glu	CTG Leu	GAC Asp 20	GGC Gly	GAC Asp	GTA Val	AAC Asn	GGC Gly 25	CAC His	AAG Lys	TTC Phe	AGC Ser	GTG Val 30	TCC Ser	GGC Gly	96
20	GAG Glu	GGC Gly	GAG Glu 35	GGC Gly	GAT Asp	GCC Ala	ACC Thr	TAC Tyr 40	GGC Gly	AAG Lys	CTG Leu	ACC Thr	CTG Leu 45	AAG Lys	TTC Phe	ATC Ile	144
25	TGC Cys	ACC Thr 50	ACC Thr	GGC Gly	AAG Lys	CTG Leu	CCC Pro 55	GTG Val	CCC Pro	TGG Trp	CCC Pro	ACC Thr 60	CTC Leu	GTG Val	ACC Thr	ACC Thr	192
30	CTG Leu 65	ACC Thr	TAC Tyr	GGC Gly	GTG Val	CAG Gln 70	TGC Cys	TTC Phe	AGC Ser	CGC Arg	TAC Tyr 75	CCC Pro	GAC Asp	CAC His	ATG Met	AAG Lys 80	240
35	CAG Gln	CAC His	GAC Asp	TTC Phe	TTC Phe 85	AAG Lys	TCC Ser	GCC Ala	ATG Met	CCC Pro 90	GAA Glu	GGC Gly	TAC Tyr	GTC Val	CAG Gln 95	GAG Glu	288
	CGC Arg	ACC Thr	ATC Ile	TTC Phe 100	TTC Phe	AAG Lys	GAC Asp	GAC Asp	GGC Gly 105	AAC Asn	TAC Tyr	AAG Lys	ACC Thr	CGC Arg 110	GCC Ala	GAG Glu	336
40	GTG Val	AAG Lys	TTC Phe 115	GAG Glu	GGC Gly	GAC Asp	ACC Thr	CTG Leu 120	GTG Val	AAC Asn	CGC Arg	ATC Ile	GAG Glu 125	CTG Leu	AAG Lys	GGC Gly	384
45	ATC Ile	GAC Asp 130	TTC Phe	AAG Lys	GAG Glu	Asp Asp	GGC Gly 135	AAC Asn	ATC Ile	CTG Leu	GGG Gly	CAC His 140	AAG Lys	CTG Leu	GAG Glu	TAC Tyr	432
50	AAC Asn 145	TAC Tyr	AAC Asn	AGC Ser	CAC His	AAC Asn 150	GTC Val	TAT Tyr	ATC Ile	ATG Met	GCC Ala 155	GAC Asp	AAG Lys	CAG Gln	AAG Lys	AAC Asn 160	480
55	GGC Gly	ATC Ile	AAG Lys	GTG Val	AAC Asn 165	TTC Phe	AAG Lys	ATC Ile	CGC Arg	CAC His 170	AAC Asn	ATC Ile	GAG Glu	GAC Asp	GGC Gly 175	AGC Ser	528
	GTG	CAG	CTC	GCC	GAC	CAC	TAC	CAG	CAG	AAC	ACC	ccc	ATC	GGC	GAC	GGC	576 2

										442								
	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly		
	CCC	GTG	CTG	CTG	CCC	GAC	AAC	CAC	TAC	СТС	»GC	ACC	CAG	יייכר	GCC	CTG	624	
5					Pro												024	
	AGC	AAA	GAC	ccc	AAC	GAG	AAG	CGC	GAT	CAC	ATG	GTC	CTG	CTG	GAG	TTC	672	
10					Asn													
					~~~	*==												
					GGG Gly												720	
	225		nia	niu	O <sub>T</sub>	230	****	Deu	Ory	MEL	235	GLU	Deu	-y-	цур	240		
15																		
	GGA	CTC	AGA	TCT	CGA	GCT	CAA	GCT	TCC	ATG	AGC	GAG	ACG	GTC	ATC	ATG	768	
	Gly	Leu	Arg	Ser	Arg	Ala	Gln	Ala	Ser	Met	Ser	Glu	Thr	Val	Ile	Met		
					245					250					255			
20	3.00	a 2 a	3.00	oma	ATC	mam	maa	200	~~~	~~~	3.00	ama.	3 PH/CI	omm	m s m	GB TH	02.6	
20					Ile												816	
	00.	014	****	260		Cyn	<b>U</b> C1	501	265	ALU	****	val	Mec	270	-1-	nap		
	GAT	GGC	AAC	AAG	CGA	TGG	CTC	CCT	GCT	GGC	ACG	GGT	CCC	CAG	GCC	TTC	864	
25	Asp	Gly	Asn	Lys	Arg	${\tt Trp}$	Leu	${\tt Pro}$	Ala	Gly	Thr	Gly	Pro	${\tt Gln}$	Ala	Phe		
			275					280					285					
	200	000	ama	03 G	N M C	ma c	ara.	220	000	200	~~~	3.3M	maa	-	~~~	amo	010	
					ATC Ile												912	
30		290	Val	0111	-10	- y -	295	ADII	110	1111	AIG	300	Der	FIIG	arg	Val		
	GTG	GGC	CGG	AAG	ATG	CAG	CCC	GAC	CAG	CAG	GTG	GTC	ATC	AAC	TGT	GCC	960	
		Gly	Arg	Lys	Met		Pro	Asp	Gln	Gln	Val	Val	Ile	Asn	Cys	Ala		
25	305					310					315					320		
35	አጥሮ	GTIC	ccc	COTT	GTC	አአር	ጥለጥ	አክሮ	CNC	ccc	אממ	ccc	220	mma	C N IT	CAC	1008	
					Val												1008	
				7	325	_,_	-1-			330		110	11011	1110	335	0111		
40	TGG	CGC	GAC	GCT	CGC	CAG	GTC	TGG	GGC	CTC	AAC	TTC	GGC	AGC	AAG	GAG	1056	
	Trp	Arg	Asp		Arg	Gln	Val	Trp		Leu	Asn	Phe	Gly		Lys	Glu		
				340					345					350				
	GAT	GCG	GCC	CAG	TTT	GCC	GCC	GGC	ATG	GCC	AGT	GCC	СТА	GAG	GCG	TTG	1104	
45					Phe													
	-		355					360					365					
					CCC												1152	
EO	Glu	-	Gly	Gly	Pro	Pro		Pro	Pro	Ala	Leu		Thr	Trp	Ser	Val		
50		370					375					380						
	CCG	AAC	GGC	כככ	TCC	כרמ	GAG	GAG	GTC	GZG	CAG	CAG	ΔΔΔ	AGG	CAG	CAG	1200	
					Ser													
	385		•			390					395		•			400		
55	_																	
•	CCC	GGC	CCG	TCG	GAG	CAC	ATA	GAG	CGC	CGG	GTC	TCC	AAT	GCA	GGA	GGC	1248	
																		•

										243							
	Pro	Gly	Pro	Ser	Glu 405		Ile	Glu	Arg	Arg 410	Val	Ser	Asn	Ala	Gly 415	Gly	
	CCA	CCT	GCT	CCC	CCC	GCT	GGG	GGT	CCA	CCC	CCA	CCA	CCA	GGA	CCT	CCC	1296
5		Pro															1250
	CCT	CCT	CCA	GGT	ccc	ccc	CCA	ccc	CCA	GGT	TTG	ccc	CCT	тса	GGG	GTC	1344
		Pro															7544
10			435					440					445		_		
		GCT															1392
	Pro	Ala 450	АТА	Ala	HIS	GIĀ	455	GTA	GTA	GIA	Pro	Pro 460	Pro	АТа	Pro	Pro	
15		130										400					
	CTC	CCG	GCA	GCA	CAG	GGC	CCT	GGT	GGT	GGG	GGA	GCT	GGG	GCC	CCA	GGC	1440
		Pro															
	465					470					475					480	
20	מיזים	acc	CCA	COM	א יויינוי	COM	CCA	aaa	777	oma.	ri co		cmc	3.00	224	a.a	
20		GCC Ala															1488
					485		<b>-</b>		_,_	490	**** 3	2,5	V 44.1	50.	495	G111	
		GAG															1536
25	Glu	Glu	Ala		Gly	Gly	Pro	Thr		Pro	ГÀЗ	Ala	Glu		Gly	Arg	
				500					505					510			
	AGC	GGA	GGT	GGG	GGA	CTC	ATG	GAA	GAG	ATG	AAC	GCC	ATG	CTG	GCC	CGG	1584
	Ser	Gly	Gly	Gly	Gly	Leu	Met	Glu	$\operatorname{Glu}$	Met	Asn	Ala	Met	Leu	Ala	Arg	
30			515					520					525				
	DCD	AGG	אאא	GCC	እሮር	CAN	הואה	ccc	ana	אאה	3 CC	ccc	אאכי	(TATE	<b>CDD</b>	TI CITI	1633
		Arg															1632
	_	530					535	2		_4		540					
35																	
		TAA															1680
	545	Asn	GIN	GII	GIU	550	GIU	ATA	Arg	Val		Ala	GIn	ser	Glu	Ser 560	
	242					330					555					360	
40	GTG	CGG	AGA	CCC	TGG	GAG	AAG	AAC	AGC	ACA	ACC	TTG	CCA	AGG	ATG	AAG	1728
	Val	Arg	Arg	Pro	Trp	Glu	Lys	Asn	Ser	Thr	Thr	Leu	Pro	Arg	Met	Lys	
					565					570					575		
	тсс	TCT	ידיריידי	TCG	GTG	<b>ACC</b>	አረጥ	TCC	GNG	אממ	(7) N	ccc	TOO	אככ	ccc	N.C.C	1776
45		Ser															1776
			_	580					585				-1-	590			
		AGT															1824
50	ser	Ser	-	Tyr	Ser	Asp	Leu		Arg	Val	Lys	Gln		Leu	Leu	Glu	
			595					600					605				
	GAG	GTG	AAG	AAG	GAA	TTG	CAG	AAA	GTG	AAA	GAG	GAA	ATC	ATT	GAA	GCC	1872
		Val															
55		610					615					620					
55	ጥጥር	GTC	כאכ	GNO	CTC	አርር	አአር	000	C C M	m/dm	ccc	ייט איני					1000
	.10	GIC	CAG	GAG	C1G	DUM	HAG	ناتاب	GGT	ICT	ccc	IGA					1908
																	2

244

Phe Val Gln Glu Leu Arg Lys Arg Gly Ser Pro 625 630 635

5 (2) INFORMATION FOR SEQ ID NO:125:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 635 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (v) FRAGMENT TYPE: internal

15

25

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15

20 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20 25 30

Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 35 40 45

Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
50 60

Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 65 70 . 75 80

Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 90 95

30 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 100 105 110

Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
115 120 . 125

Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 35 130 135 140

Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 145 150 155 160

Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 165 170 175

40 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 180 185 190

Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 195 200 205

Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 45 210 215 220

Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
225 230 235 240

Gly Leu Arg Ser Arg Ala Gln Ala Ser Met Ser Glu Thr Val Ile Met
245 250 255

50 Ser Glu Thr Val Ile Cys Ser Ser Arg Ala Thr Val Met Leu Tyr Asp 260 265 270

Asp Gly Asn Lys Arg Trp Leu Pro Ala Gly Thr Gly Pro Gln Ala Phe 275 280 285

Ser Arg Val Gln Ile Tyr His Asn Pro Thr Ala Asn Ser Phe Arg Val 55 290 295 300

Val Gly Arg Lys Met Gln Pro Asp Gln Gln Val Val Ile Asn Cys Ala

	305					310					315					320
	Ile	Val	Arg	Gly	Val 325	Lys	Tyr	Asn	Gln	Ala 330	Thr	Pro	Asn	Phe	His 335	Gln
5	Trp	Arg	Авр	Ala 340	Arg	Gln	Val	Trp	Gly 345	Leu	Asn	Phe	Gly	Ser 350	ГÀЗ	Glu
	Asp	Ala	Ala 355	Gln	Phe	Ala	Ala	Gly 360	Met	Ala	Ser	Ala	Leu 365	Glu	Ala	Leu
	Glu	Gly 370	Gly	Gly	Pro	Pro	Pro 375	Pro	Pro	Ala	Leu	Pro 380	Thr	Trp	Ser	Val
10	385		Gly			390					395		-	_		400
•	Pro	Gly	Pro	Ser	Glu 405	His	Ile	Glu	Arg	Arg 410	Val	Ser	Asn	Ala	Gly 415	Gly
15	Pro	Pro	Ala	Pro 420	Pro	Ala	Gly	Gly	Pro 425	Pro	Pro	Pro	Pro	Gly 430	Pro	Pro
	Pro	Pro	Pro 435	Gly	Pro	Pro	Pro	Pro 440	Pro	Gly	Leu	Pro	Pro 445	Ser	Gly	Val
		450	Ala				455		_	=		460				
20	Leu 465	Pro	Ala	Ala	Gln	Gly 470	Pro	Gly	Gly		Gly .475	Ala	Gly	Ala	Pro	Gly 480
	Leu	Ala	Ala	Ala	Ile 485	Ala	Gly	Ala	Lys	Leu 490	Arg	Lys	Val	Ser	Lys 495	Gln
25	Glu	Glu	Ala	Ser 500	Gly	Gly	Pro	Thr	Ala 505	Pro	ГÀЗ	Ala	Glu	Ser 510	Gly	Arg
	Ser	Gly	Gly 515	Gly	Gly	Leu	Met	Glu 520	Glu	Met	Asn	Ala	Met 525	Leu	Ala	Arg
	Arg	Arg 530	Lys	Ala	Thr	Gln	Val 535	Gly	Glu	Lys	Thr	Pro 540	Lys	Asp	Glu	Ser
30	Ala 545	Asn	Gln	Glu	Glu	Pro 550	Glu	Ala	Arg	Val	Pro 555	Ala	Gln	Ser	Glu	Ser 560
	Val	Arg	Arg	Pro	Trp 565	Glu	ГÀЗ	Asn	Ser	Thr 570	Thr	Leu	Pro	Arg	Met 575	Lys
35	Ser	Ser	Ser	Ser 580	Val	Thr	Thr	Ser	Glu 585	Thr	Gln	Pro	Cys	Thr 590	Pro	Ser
	Ser	Ser	<b>Asp</b> 595	Tyr	Ser	Asp	Leu	Gln 600	Arg	Val	ГÀа	Gln	Glu 605	Leu	Leu	Glu
	Glu	Val 610	Lys	ГÀа	Glu	Leu	Gln 615	ГÀа	Val	ГÀв	Glu	Glu 620	Ile	Ile	Glu	Ala
40	Phe 625		Gln	Glu	Leu	Arg 630	Lys	Arg	Gly	Ser	Pro 635					
			(2	) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	126:					
45		,	4 \ G	-	MOD	CITA D	3 C(D)	D T 0M	<b>TGG</b> .							
40		`		LEN	GTH:	132 ucle	9 ba	se p								
			(C)						e							
						Y: 1										
50		(	ii)	MOLE	CULE	TYP	E: c	DNA								
			ix)													
55						EY: ON:				nce						
						INFO										

246

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

		(3		TOWAL	314 C15	ייייייייייייייייייייייייייייייייייייייי	LKIP	LION	SEÇ	עד ג	140:1	120:					
5				AAG Lys													48
10	_			GAC Asp 20													96
15				GGC Gly													144
				GGC Gly												ACC Thr	192
20				GGC Gly													240
25				TTC Phe													288
30	Arg	Thr	Ile	TTC Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	ГÀв	Thr	Arg 110	Ala	Glu	336
35	Val	Lys	Phe 115	GAG Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	ГÀЗ	Gly	384
40	Ile	Asp 130	Phe	AAG Lys	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr	432
40	Asn 145	Tyr	Asn	AGC	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Gln	Lys	Asn 160	480
45	Gly	Ile	Lys	GTG Val	Asn 165	Phe	Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser	528
50	Val	Gln	Leu	GCC Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly	576
55	Pro	Val	Leu 195	CTG Leu CCC	Pro	Asp	Asn	His 200	Tyr	Leu	Ser	Thr	Gln 205	Ser	Ala	Leu	624 672
	AGC	AAA	GAC	درد	AAC	GAG	DAM	CGC	GAT	CAC	MIG	GIC	CIG	C16	GAG	110	012

									•	_7,							
	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg	Asp	His		Val 220	Leu	Leu	Glu	Phe	
5			GCC Ala							Met							720
10			AGA Arg														768
15			ATT Ile														816
15			AGC Ser 275														864
20			TAT Tyr														912
25			TGG Trp														960
30			TAC Tyr														1008
05			GAT Asp														1056
35			TTC Phe 355						Ile								1104
40			CGG					Thr					Ala				1152
45		Glu	CCG Pro				Glu					Met				ATT Ile 400	1200
50						Met					Lys					GTG Val	1248
					: Glu					, Ala					Arg	CGT Arg	1296
55	GG	AA E	KAA E	AAA	A TCT	r GG:	TGC	CT	r gto	TTO	TG!	<b>A</b> .					1329 247

248

Gly Lys Lys Ser Gly Cys Leu Val Leu 435 5 (2) INFORMATION FOR SEQ ID NO:127: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 442 amino acids (B) TYPE: amino acid 10 (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:127: Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 10 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 25 55 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 75 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 30 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 35 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 170 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 40 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 45 -220 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 Gly Leu Arg Ser Arg Ala Gln Ala Ser Met Ala Ala Ile Arg Lys Lys 250 245 Leu Val Ile Val Gly Asp Gly Ala Cys Gly Lys Thr Cys Leu Leu Ile 50

Val Phe Ser Lys Asp Gln Phe Pro Glu Val Tyr Val Pro Thr Val Phe
275
280
285
Glu Asn Tyr Val Ala Asp Ile Glu Val Asp Gly Lys Gln Val Glu Leu

Ala Leu Trp Asp Thr Ala Gly Gln Glu Asp Tyr Asp Arg Leu Arg Pro

295

	305					310					315					320			
	Leu	Ser	Tyr	Pro	Asp 325	Thr	Asp	Val	Ile	Leu 330	Met	Сув	Phe	Ser	Ile 335	Asp			
5			-	340		Glu			345					350					
	_		355	_		Asn		360					365						
		370				Glu	375					380							
10		Glu	Pro	Val	Lys	Pro	Glu	Glu	Gly	Arg	Asp 395	Met	Ala	Asn	Arg	11e			
	385 Gly	Ala	Phe	Gly	Tyr 405	390 Met	Glu	Сув	Ser	Ala 410		Thr	Lys	Asp	Gly 415				
15	Arg	Glu	Val	Phe 420	Glu	Met	Ala	Thr	Arg 425	Ala	Ala	Leu	Gln	Ala 430	Arg	Arg			
	Gly	Lys	Lys 435	Lys	Ser	Gly	Сув	Leu 440	Val	Leu									
20 '			(2)	) IN	FORM	ATION	FOR	SEC	) ID	NO:1	L <b>28</b> :								
40		(:	(A)	LEN	STH:	CHARA 1140 iclei	) bas	e pa	4										
25						ONESS Y: li			•		٠								
		-	. :	MOLE FEAT		TYPE	G: CI	AMO											
30			(B	) LO	CATI	EY: C ON: 1 INFOR	11	1137	equer	ice									
35		(:	xi) :	SEQU	ENCE	DESC	CRIPT	CION	: SE(	Q ID	NO: 3	128:							
•						TCT Ser											48	,	
40						GAC Asp											96		
<b>4</b> 5	-					ACG Thr											144		
50																ГЛЗ	192		
																CCÁ Pro 80	240		
55	GAG	CGA	GGC	: AAG	ATC	AGA	GTG	CAC	AAG	ATC	TCC	AAC	GTC	AAC	. AAG	GCC	288	249	

	Glu	Arg	Gly	Lys	Met 85	Arg	Val	His	Lys	Ile 90	Ser	Asn	Val	Asn	Lys 95	Ala		
5			TTC Phe														336	
10			ATC Ile 115														384	
15	-		ATC Ile								•						432	
10			GAG Glu														480	
20			GTA Val														528	
25			ACC Thr														576	
30			CCC Pro 195														624	
25			TGC Cys													*	672	
35			TCC Ser														720	
40		_	GAC Asp														768	
45			ACC Thr														816	
50			GGC Gly 275						Lys								864	
re			GTC Val					Asp					Gly				912	
55	AAC	TTC	AAG	ATC	CGC	CAC	AAC	ATC	GAG	GAC	GGC	AGC	GTG	CAG	CTC	GCC	960	250

					•				:	251		•					
	305					310					315				Leu	320	
5															CTG Leu 335		1008
10															GAC Asp		1056
															GCC Ala		1104
15		ATC Ile 370										TAA		•			1140
20			(2)	INI	FORM	ATIO	1 FOI	R SE(	) ID	NO:	L29:						
25		i)	(A) (B) (C)	LENG TYPI STRA	ETH: E: ar ANDEI	CHARA 379 mino ONESS	amin acio 3: si	no ad i ingle	cids								
30		(1	/) FI	RAGMI	ENT :	TYPI FYPE DES(	: int	erna	al	O ID	NO:	129:					
35	Met 1												Met	Gln	Pro 15	Glu	
00	Glu			20	Arg				25	Asp				30	Lys		
40		-	35					40	-				45	_	Lys		
	Leu	50				Glu	55				Glu	60			Гуs	Pro	
45	65 Glu	Arg	Gly	Lys	Met 85		Val	His	Lys	Ile 90	75 Ser	Asn	Val	Asn	Lys 95	80 Ala	
				100	Ala	Ser		_	105					110		Ala	
50			115		_	·		120	_				125			Trp	
00		130			_	_	135					140				Asp	
	145		v∍l	Agn	Glv	150	ГÀв	Phe	Ser	Wal.	155		Glu	Glv	. Glu	160	
55	GIY	vab	Val	21014	165			1 110	DCI	170		Orl		<b></b> ,	175		

				180					185					190				
,	Lys	Leu	Pro 195	Val	Pro	Trp	Pro	Thr 200	Leu	Val	Thr	Thr	Leu 205	Thr	Tyr	Gly		
5		Gln 210	Сув			_	215	Pro	_			220	Gln		_			
	Phe 225	ГЛЗ	Ser	Ala	Met	Pro 230	Glu	Gly	Tyr	Val	Gln 235	Glu	Arg	Thr	Ile	Phe 240		
		Lys	Авр	Asp	Gly		Tyr	Lys	Thr	Arg		Glu	Val	Lys	Phe			
10	Glv	Asp	Thr	T.en	245 Val	Agn	Ara	Tle	Glu-	250 Lev	Lva	Glv	Tle	Δan	255 Dhe	Iwa		
. •				260					265		_,,	0-1	-10	270		-,-		
		Asp	275				_	280	•			-	285	-				
15	His	Asn 290	Val	Tyr	Ile	Met	Ala 295	qzA	Lys	Gln	Lys	Asn 300	Gly	Ile	Lys	Val		
		Phe	Lys	Ile	Arg	His 310	Asn	Ile	Glu	qeA	Gly 315	Ser	Val	Gln	Leu	Ala 320		
	305 Asp	His	Tyr	Gln			Thr	Pro	Ile			Gly	Pro	Val				
20	Pro	Asp	Asn		325 Tyr	Leu	Ser	Thr		330 Ser	Ala	Leu	Ser	-	335 Asp	Pro		
	Asn	Glu	Lys	340 Arg	Asp	His	Met	Val	345 Leu	Leu	Glu	Phe	Val	350 Thr	Ala	Ala		
	<b>~</b> 1	T1.0	355	T 033	C1	Mot	7.00	360	Y 033		Tara		365					
25	GIĄ	11e 370	IIII	Leu	GIŸ	MEC	375	GIU	пеп	TÀT	пув							
			(2)	INI	FORM	ATIO1	v FOI	R SE	Q ID	NO:	130:							
		( i	i) si	auos E	ICE (	THAR	ACTE	RIST'	tcs:									
30		,-	(A)	LENG	STH:	351	6 bas	se pa										
							ic ad S: s:		9									
			(D)	TOP	orog.	Y: 1:	inea	r										
35				MOLE PEAT		TYP	Ē: CI	DNA										
							Codi	_	eque	nce								
40							l: RMAT:											
		1-	ri) :	SEOII	RNCE	DES	CRIP'	ттом	. SE	מז ח	NO.	120.						
				_														
45		GTG Val															48	
	1			-	5					10	-				15			
																GGC	96	
50	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	ГÀв	Phe	Ser	Val 30	Ser	Gly		
•	GAG	ממר	GAG	ccr	תמ	י פכר	. ארר	ייז מייזי	מממ	ממ	י רידים	ארר	Carca	אמג	. <b></b>	ATC	144	
			Glu					Tyr					Leu			Ile		
55			35					40					45					
	TGC	ACC	ACC	GGC	AAG	CTG	ccc	GTG	ccc	TGG	CCC	ACC	CTC	GTG	ACC	ACC	192	
																		252

										200							
	Сув	Thr 50	Thr	Gly	ГÀЗ	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr	
5	CTG Leu 65	ACC Thr	TAC Tyr	GGC Gly	GTG Val	CAG Gln 70	TGC Cys	TTC Phe	AGC Ser	CGC Arg	TAC Tyr 75	CCC Pro	GAC Asp	CAC His	ATG Met	AAG Lys	240
10		CAC His															288
15		ACC Thr															336
.0		AAG Lys															384
20		GAC Asp 130															432
25		TAC Tyr															480
30		ATC Ile															528
35		CAG Gln															576
		GTG Val															624
40		AAA Lys 210															672
45		ACC Thr															720
50		CTC Leu															768
EE		GGC Gly															816
55	GAG	CTT	GAC	TTC	TCC	ATC	CTC	TTC	GAC	TAT	GAG	TAT	TTG	AAT	CCG	AAC	864

										254								
	Glu	Leu	Asp 275	Phe	Ser	Ile	Leu	Phe 280	Asp	Tyr	Glu	Tyr	Leu 285	Asn	Pro	Asn		
5					AAT Asn												912	
10					GAT Asp												960	
15		_			TCT Ser 325												1008	
13					CAG Gln												1056	
20					CCT Pro												1104	
25					CCC Pro			•									1152	
30					GCC Ala												1200	
35					GAG Glu 405												1248	
33					TCT Ser												1296	
40					GTC Val												1344	
45					AAC Asn												1392	
50					CGA Arg												1440	
<b></b>					CCC Pro- 485												1488	
55 .	AAG	CGG	AGG	CAT	TCG	TGC	GCC	GAG	GCC	TTG	GTT	GCC	CTG	CCG	ccc	GGA	1536	2

									•	دِين							
	Lys	Arg	Arg	His 500	Ser	Cys	Ala	Glu	Ala 505	Leu	Val	Ala	Leu	Pro 510	Pro	Gly	
5	-		Pro		CGC Arg							_					1584
					GAC			TCC					CCC				1632
10	Val	530	PIO	GIU	Asp	nis	535	ser	PIO	ALA	GIÀ	540	PIO	PIO	vai	AId	
15					ATC Ile												1680
13					CCC Pro 565												1728
20					GCC Ala												1776
25					TTC Phe												1824
30					TCC Ser												1872
25					ATT Ile												1920
35					TGG Trp 645												1968
40					CAG Gln												2016
45				Arg	GGG Gly									His		_	2064
50					GGC Gly			Glu					Gly			ATC Ile	2112
		Ile					Glu					Pro				TAC Tyr 720	2160
55	CAG	GTG	CAC	: CGA	ATC	ACG	GGG	AAA	ACT	GTC	ACC	ACC	: ACC	: AGC	TAT	GAG	2208 2!

256

									•	200								
	Gln	Val	His	Arg	Ile 725	Thr	Gly	Lys	Thr	Val 730	Thr	Thr	Thr	Ser	Tyr 735	Glu		
	ממ	מדמ	GTG.	GGC	AAC	ACC	ΔΔΔ	GTC	CTG	GAG	ΔΤΟ	CCC	ተጥር፤	GAG	כככ	ΔΔΔ	2256	
5					Asn													
J	_,,			740			-, -		745	<b></b>				750		-,-		
	AAC	AAC	ATG	AGG	GCA	ACC	ATC	GAC	TGT	GCG	GGG	ATC	TTG	AAG	CTT	AGA	2304	
	Asn	Asn	Met	Arg	Ala	Thr	Ile	Asp	Cys	Ala	Gly	Ile	Leu	Lys	Leu	Arg		
10			755					760					765					
					GAG												2352	
	Asn		Asp	TTE	Glu	Leu		ГÄŝ	GTA	GIU	Thr		IIe	GTA	Arg	ràe		
15		770					775					780					•	
13	AAC	ACG	CGG	GTG	AGA	CTG	GTT	TTC	CGA	GTT	CAC	ATC	CCA	GAG	TCC	AGT	2400	
					Arg												2200	
	785		3		5	790			3		795					800		
	•																	
20	GGC	AGA	ATC	GTC	TCT	TTA	CAG	ACT	GCA	TCT	AAC	CCC	ATC	GAG	TGC	TCC	2448	
	Gly	Arg	Ile	Val	Ser	Leu	Gln	Thr	Ala		Asn	Pro	Ile	Glu	_	Ser		
					805					810					815			
	a. a	-	mam		an a	G2.G	ama	000	3.000	amm	<b>a.</b>	303	<b>~</b> ~ ~ ~	a.a	202	03.0	2406	
25					CAC His												2496	
25	GLII	ALG	Ser	820	ura	GIU	пса	FLO	825	Val	GIU	Arg	GIII	830	IIII	rob		
									02.5									
	AGC	TGC	CTG	GTC	TAT	GGC	GGC	CAG	CAA	ATG	ATC	CTC	ACG	GGG	CAG	AAC	2544	
	Ser	Cys	Leu	Val	Tyr	Gly	Gly	Gln	${\tt Gln}$	Met	Ile	Leu	Thr	Gly	Gln	Asn		
30			835					840					845					
					TCC												2592	
	Pne	850	ser	GIU	Ser	гув	855	vaı	hue	Thr	GIU	860 TÀB	Thr	unr	Asp	GIA		
35		950					033					860						
00	CAG	CAA	ATT	TGG	GAG	ATG	GAA	GCC	ACG	GTG	GAT	AAG	GAC	AAG	AGC	CAG	2640	
					Glu													
	865			_		870					875	_	-	_		880		
40					TTT												2688	
	Pro	Asn	Met	Leu	Phe	vai	GIu	lle	Pro		Tyr	Arg	Asn	гÃв		тте		
					885					890					895			
	CGC	ACA	ССТ	GTA	ААА	GTG	AAC	ייייכי	TAC	GTC	ATC	דעמ	GGG	AAG	AGA	AAA	2736	
45																Lys		
	5			900	•				905					910		•		
																AAG	2784	
	Arg	Ser			Gln	His	Phe		-	His	Pro	Val		Ala	Ile	Lys		
50			915					920					925					
	200	<b>030</b>	~~~	700	מואנים	(13.5	m v m	C2 C	000	y Cam	Cmc	አመሳ	Tro-c	700	CCC	ACC	2832	
																Thr	2032	
		930					935	-		~ - 4 *		940	_					
55																		
	CAT	GGA	GGC	CTG	GGG	AGC	CAG	CCT	TAC	TAC	ccc	CAG	CAC	CCG	ATG	GTG	2880	
																		2

	His 945	Gly	Gly	Leu	Gly	Ser 950	Gln	Pro	Tyr	Tyr	Pro 955	Gln	His	Pro	Met	Val 960	
5	GCC Ala																2928
10					CTC Leu												2976
15					CTC Leu		Gln					Leu					3024
	Leu				CAG Gln	Pro					Ala						3072
20					TCT Ser					Ala					Gln		3120
25				Leu	CAC His 1045				Thr					Ser			3168
30			Tyr		CCC Pro			Gln					Gly				3216
		Phe			ATC Ile		Tyr					Ala			_	_	3264
35	Arg				CCC Pro	Pro					Gln						3312
40		Tyr			GTC Val					Asn					Arg		3360
45				Gly	CCC Pro 1125	Pro			Asp		Lys			Leu			3408
50			Thr		Lys			Gln		Leu			Thr		Leu	GAT Asp	3456
				Glu					Glu					Pro		AGA Arg	3504
55	AAT	CAG	ACG	TAA													3516 257

258

•

Asn Gln Thr 1170

5 (2) INFORMATION FOR SEQ ID NO:131: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 1171 amino acids (B) TYPE: amino acid 10 (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:131: Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 20 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 40 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 25 55 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 75 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 30 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 35 135 140 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 170 40 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 45 215 220 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 Gly Leu Arg Ser Arg Ala Met Asn Ala Pro Glu Arg Gln Pro Gln Pro 250 Asp Gly Gly Asp Ala Pro Gly His Glu Pro Gly Gly Ser Pro Gln Asp 50 265 Glu Leu Asp Phe Ser Ile Leu Phe Asp Tyr Glu Tyr Leu Asn Pro Asn 280 Glu Glu Glu Pro Asn Ala His Lys Val Ala Ser Pro Pro Ser Gly Pro 55 295

Ala Tyr Pro Asp Asp Val Met Asp Tyr Gly Leu Lys Pro Tyr Ser Pro

									• •	409						
	305					310					315					320
	Leu	Ala	Ser	Leu	Ser 325	Gly	Glu	Pro	Pro	Gly 330	Arg	Phe	Gly	Glu	Pro 335	Asp
5	Arg	Val	Gly	Pro 340	Gln	Lys	Phe	Leu	Ser 345	Ala	Ala	Lys	Pro	Ala 350	Gly	Ala
	Ser	Gly	Leu 355	Ser	Pro	Arg	Ile	Glu 360	Ile	Thr	Pro	Ser	His 365	Glu	Leu	Ile
	Gln	Ala 370	Val	Gly	Pro	Leu	Arg 375	Met	Arg	Asp	Ala	380 380	Leu	Leu	Val	Glu
10	385	Pro				390					395	_				400
		Pro			405					410					415	
15		Ser	_	420					425					430		_
		Ser	435					440					445			
20	•	Gln 450 Met					455			-		460	_			
20	465	Ser				470					475					480
		Arg			485					490					495	
25	-	Ser	_	500					505					510		
		Ala	515		_		_	520					525			
30		530 Ser			_		535				-	540				
	545	Cys				550	_				.555				_	560
		- Val			565					570					575	
35	Pro	Ala	Val	580 Glu	Phe	Leu	Gly	Pro	585 Cys	- Glu	Gln	Gly	Glu	590 Arg	Arg	Asn
	Ser	Ala	595 Pro	Glu	Ser	Ile	Leu	600 Leu	Val	Pro	Pro	Thr	605 Trp	Pro	Lys	Pro
40	Leu	610 Val	Pro	Ala	Ile	Pro	615 Ile	Сув	Ser	Ile	Pro	620 Val	Thr	Ala	Ser	Leu
	625 Pro	Pro	Leu	Glu	Trp	630 Pro	Leu	Ser	Ser	Gln	635 Ser	Gly	Ser	Tyr	Glu	640 Leu
	Arg	Ile	Glu		645 Gln	Pro	Lys	Pro	His	650 His	Arg	Ala	His	Tyr	655 Glu	Thr
45	Glu	Gly		660 Arg	Gly	Ala	Val	_	665 Ala	Pro	Thr	Gly		670 His	Pro	Val
	Val		675 Leu	His	Gly	Tyr		680 Glu	Asn	Lys	Pro		685 Gly	Leu	Gln	Ile
50		690 Ile	Gly	Thr	Ala	_	695 Glu	Arg	Ile	Leu	-	700 Pro	His	Ala	Phe	Tyr 720
	705 Gln	Val	His	Arg	Ile 725	710 Thr	Gly	Lys	Thr	Val 730	715 Thr	Thr	Thr	Ser	Tyr 735	Glu
55	Lys	Ile	Val	Gly 740		Thr	Lys	Val	Leu 745		Ile	Pro	Leu	Glu 750		Lys
	Asn	Asn	Met		Ala	Thr	Ile	Asp		Ala	Gly	Ile	Leu		Leu	Arg

260

			755					760					765			
-	Asn	Ala 770	Двр	Ile	Glu	Leu	Arg 775	ГÀЗ	Gly	Glu	Thr	Asp 780	Ile	Gly	Arg	Lys
5	Asn 785	Thr	Arg	Val	Arg	Leu 790	Val	Phe	Arg	Val	His 795	Ile	Pro	Glu	Ser	Ser 800
	Gly	Arg	Ile	Val	Ser 805	Leu	Gln	Thr		Ser 810	Asn	Pro	Ile	Glu	Cys 815	Ser
	Gln	Arg	Ser	Ala 820	His	Glu	Leu	Pro	Met 825	Val	Glu	Arg	Gln	Asp 830	Thr	Asp
10	Ser	Сув	Leu 835	Val	Tyr	Gly	Gly	Gln 840	Gln	Met	Ile	Leu	Thr 845	Gly	Gln	Asn
	Phe	Thr 850	Ser	Glu	Ser	ГÀв	Val 855	Val	Phe	Thr	Glu	Lys 860	Thr	Thr	Asp	Gly
15	Gln 865	Gln	Ile	Trp	Glu	Met 870	Glu	Ala	Thr	Val	Asp 875	Lys	Asp	ГÀЗ	Ser	Gln 880
	Pro	Asn	Met	Leu	Phe 885	Val	Glu	Ile	Pro	Glu 890	Tyr	Arg	Asn	Lys	His 895	Ile
	Arg	Thr	Pro	Val 900	Lys	Val	Asn	Phe	Tyr 905	Val	Ile	Asn	Gly	Lys 910	Arg	Lys
20	Arg	Ser	Gln 915	Pro	Gln	His	Phe	Thr 920	Tyr	His	Pro	Val	Pro 925	Ala	Ile	Lys
	Thr	Glu 930	Pro	Thr	Asp	Glu	Tyr 935	qaA	Pro	Thr	Leu	Ile 940	Сув	Ser	Pro	Thr
25	His 945	Gly	Gly	Leu	Gly	Ser 950	Gln	Pro	Tyr	Tyr	Pro 955	Gln	His	Pro	Met	Val 960
	Ala	Glu	Ser	Pro	Ser 965	Сув	Leu	Val	Ala	Thr 970	Met	Ala	Pro	Сув	Gln 975	Gln
	Phe	Arg	Thr	Gly 980	Leu	Ser	Ser	Pro	Asp 985	Ala	Arg	Tyr		Gln 990	Gln	Asn
30	Pro	Ala	Ala 995	Val	Leu	Tyr		Arg	Ser	ГÀЗ	Ser				Ser	Leu
		Gly 1010	Tyr	Gln	Gln		Ala 1015	Leu	Met	Ala		Pro 1020	Leu	Ser	Leu	Ala
	Asp	Ala	His	Arg	Ser	Val	Leu	Val	His	Ala	Gly	Ser	Gln	Gly	Gln	Ser
35	025	_				1030					1035	_				1040
			Leu	:	1045				:	1050				:	1055	
	Ile	His	Tyr	Ser 1060	Pro	Thr	Asn		Gln 1065	Leu	Arg	Cys		Ser 1070	His	Gln
40	Glu		Gln 1075		Ile	Met	_			Asn	Phe				Thr	Thr
	_		Gly	Pro	Pro			Ser	Gln	Gly				Ser	Pro	Gly
	Ser	Tyr	Pro	Thr	Val				Gln	Asn	Ala	Thr	Ser	Gln	Arg	Ala
45	105					1110					1115					1120
	Ala	ГÀЗ	Asn		Pro 1125		Val	Ser		Gln 1130	_	Glu	Val		Pro 1135	
	Gly	Val	Thr	Ile 1140		Gln	Glu		Asn 1145		Asp	Gln		Tyr 1150	Leu	Asp
50	Asp		Asn 1155		Ile	Ile		Lys 1160		Phe	Ser		Pro 1165		Ala	Arg
		Gln 1170	Thr													

55 (2) INFORMATION FOR SEQ ID NO:132:

5		(i	(A) (B) (C)	LENG TYPE STRA	CE C TH: : nu NDED LOGY	3546 clei NESS	bas c ac : si	e pa id ngle	irs								
			i) M x) F		ULE RE:	TYPE	: cD	NA									
10			(B)	roc	E/KE ATIO ER I	N: 1	3	543	quen	ice							
15		(х	i) S	EQUE	NCE	DESC	RIPT	ION:	SEÇ	DI	NO : 1	.32:					
		AAC Asn															48
20		CAC His															96
25		TTC Phe															144
30		AAG Lys 50														_	192
35		GAC Asp															240
33		CCC Pro															288
40		CTG Leu															336
45	_	GAG Glu															384
50		ATG Met 130													_	_	432
55		GCC Ala					Phe										480
55	TAC	CGC	GAG	CCG	CTT	TGC	TTG	AGC	ccc	GCT	AGC	AGC	GGC	TCC	TCT	GCC	528

									:	262							
	Tyr	Arg	Glu	Pro	Leu 165	Сув	Leu	Ser	Pro	Ala 170	Ser	Ser	Gly	Ser	Ser 175	Ala	
5						ACC Thr											576
10						CCC Pro	qaA										624
15						CCC Pro											672
						AGC Ser 230											720
20						TCA Ser											768
25						GCC Ala											816
30						CAG Gln											864
35						TAC Tyr											912
30						CTC Leu 310											960
40						AGC Ser											1008
45						CCT Pro				Tyr						CTG Leu	1056
50				Glu					Arg					Glu		ATC Ile	1104
EF			Val					Pro					Pro			CCC Pro	1152
55	ATC	TGC	AGC	ATC	CCA	GTG	ACT	GCA	TCC	CTC	CCI	CCA	. CTI	' GAG	TGG	CCG	1200

										200							
	Ile 385	Cys	Ser	Ile	Pro	Val 390	Thr	Ala	Ser	Leu	Pro 395	Pro	Leu	Glu	Trp	Pro 400	
5	CTG Leu	TCC Ser	AGT Ser	CAG Gln	TCA Ser 405	GGC Gly	TCT Ser	TAC Tyr	GAG Glu	CTG Leu 410	CGG Arg	ATC Ile	GAG Glu	GTG Val	CAG Gln 415	CCC Pro	1248
10	AAG Lys	CCA Pro	CAT His	CAC His	CGG Arg	GCC Ala	CAC His	TAT Tyr	GAG Glu 425	ACA Thr	GAA Glu	GGC Gly	AGC Ser	CGA Arg 430	GGG Gly	GCT Ala	1296
	GTC Val	AAA Lys	GCT Ala 435	CCA Pro	ACT Thr	GGA Gly	GGC Gly	CAC His	CCT	GTG Val	GTT Val	CAG Gln	Leu	CAT	GGC Gly	TAC Tyr	1344
15			430					440					445				
	ATG Met	GAA Glu 450	AAC Asn	AAG Lys	CCT Pro	CTG Leu	GGA Gly 455	CTT Leu	CAG Gln	ATC Ile	TTC Phe	ATT Ile 460	GGG Gly	ACA Thr	GCT Ala	GAT Asp	1392
20	GAG Glu 465	CGG Arg	ATC Ile	CTT Leu	AAG Lys	CCG Pro 470	CAC His	GCC Ala	TTC Phe	TAC Tyr	CAG Gln 475	GTG Val	CAC His	CGA Arg	ATC Ile	ACG Thr 480	1440
25	GGG Gly	AAA Lys	ACT Thr	GTC Val	ACC Thr 485	ACC Thr	ACC Thr	AGC Ser	TAT Tyr	GAG Glu 490	AAG Lys	ATA Ile	GTG Val	GGC Gly	AAC Asn 495	ACC Thr	1488
30	Lys Lys	GTC Val	CTG Leu	GAG Glu 500	ATC Ile	CCC Pro	TTG Leu	GAG Glu	CCC Pro 505	AAA Lys	AAC Asn	AAC Asn	ATG Met	AGG Arg 510	GCA Ala	ACC Thr	1536
35	ATC Ile	GAC Asp	TGT Cys 515	GCG Ala	GGG Gly	ATC Ile	TTG Leu	AAG Lys 520	CTT Leu	AGA Arg	AAC Asn	GCC Ala	GAC Asp 525	ATT Ile	GAG Glu	CTG Leu	1584
	CGG Arg	AAA Lys 530	GGC Gly	GAG Glu	ACG Thr	GAC Asp	ATT Ile 535	GGA Gly	AGA Arg	AAG Lys	AAC Asn	ACG Thr 540	CGG Arg	GTG Val	AGA Arg	CTG Leu	1632
40	GTT Val 545	TTC Phe	CGA Arg	GTT Val	CAC His	ATC Ile 550	CCA Pro	GAG Glu	TCC Ser	AGT Ser	GGC Gly 555	AGA Arg	ATC Ile	GTC Val	TCT Ser	TTA Leu 560	1680
45					AAC Asn 565												1728
50					GAA Glu												1776
RE					ATC Ile												1824
55	GTT	GTG	TTT	ACT	GAG	AAG	ACC	ACA	GAT	GGA	CAG	CAA	ATT	TGG	GAG	ATG	1872

										204							
	Val	Val 610	Phe	Thr	Glu	Lys	Thr 615	Thr	Asp	Gly	Gln	Gln 620	Ile	Trp	Glu	Met	
5				GTG Val													1920
10				GAA Glu													1968
45				GTC Val 660													2016
15				CAC His													2064
20				ACT Thr													2112
25				TAC Tyr													2160
30				ACC Thr													2208
35				GCC Ala 740													2256
	_			AAG Lys													2304
40				GCC Ala	_												2352
45				GCC Ala													2400
50				AAC Asn													2448
55				CTG Leu 820													2496
	TAC	TGC	GAG	AAT	TTC	GCA	CCA	GGC	ACC	ACC	AGA	CCT	GGC	CCG	CCC	CCG	2544

	Tyr	Cys	Glu 835	Asn	Phe	Ala	Pro	Gly 840	Thr	Thr	Arg	Pro	Gly 845	Pro	Pro	Pro	
	GTC	AGT	CAA	GGT	CAG	AGG	CTG	AGC	CCG	GGT	TCC	TAC	ccc	ACA	GTC	יויידע	2592
5		Ser															
		850		_		_	855			-		860					
		CAG Gln															2640
10	865	GIII	GIII	Abii	Ата	870	ser	GTII	Arg	ATG	B75	пув	ASII	GIY	PIO	880	
										•	0.0						
	GTC	AGT	GAC	CAA	AAG	GAA	GTA	TTA	CCT	GCG	GGG	GTG	ACC	ATT	AAA	CAG	2688
	Val	Ser	Asp	Gln		Glu	Val	Leu	Pro		Gly	Val	Thr	Ile	_	Gln	
15					885					890					895		
10	GAG	CAG	AAC	TTG	GAC	CAG	ACC	TAC	TTG	GAT	GAT	GTT	AAT	GAA	ATT	ATC	2736
		Gln															
				900					905					910			
20	1.00		a.a	mmm	max	003		~~				<b>63.</b> 6			> ===	ama	2504
20		AAG Lys															2784
		_, _	915			<b>-</b>		920		9	1,011	<b>Q</b>	925	411-9		204	
		TCG		•													2832
25	GIn	Ser 930	Thr	Val	Pro	Arg	A1a 935	Arg	Asp	Pro	Pro		Ala	Thr	Met	Val	
		230					733					940					
	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	GTC	GAG	2880
		Lys	Gly	Glu	Glu		Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	Val		
30	945					950					955					960	
	CTG	GAC	GGC	GAC	GTA	AAC	GGC	CAC	AAG	TTC	AGC	GTG	TCC	GGC	GAG	GGC	2928
		Asp	_		_		_	_		_		_		_	_		
					965					970					975		
35	~~~	<b>a</b> aa	~~ m		3.00	m	~~~				-			,	<b>500</b>	200	2076
		GGC Gly															2976
	0_0	<b>4</b> -7	·wp	980		-7-	01,	<b></b> , _	985		200	<b>171</b>	1110	990	ψ, D		
40		GGC															3024
	Tnr	Gly	ьув 995	Leu	Pro	vaı		Trp 1000	Pro	Thr	Leu		Thr 1005	Thr	ren	Tnr	
			,,,				•	1000	٠.				1005				
	TAC	GGC	GTG	CAG	TGC	TTC	AGC	CGC	TAC	CCC	GAC	CAC	ATG	AAG	CAG	CAC	3072
45	_	Gly	Val	Gln	Cys			Arg	Tyr	Pro	Asp	His	Met	Lys	Gln	His	
		1010					1015					1020	•				
	GAC	TTC	TTC	AAG	TCC	GCC	ATG	ccc	GAA	GGC	TAC	GTC	CAG	GAG	CGC	ACC	3120
		Phe															
50	1025					1030					1035					1040	
	B MC	mma	mma	220	CAC	a»a	000	220	ma a	330	7.00	000	<i>-</i>	ara.	ama	N N C	21.60
		TTC Phe															3168
				_	1045	_	1		-	1050		3			1055	_	
55																	_
	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAC	CGC	ATC	GAG	CTG	AAG	GGC	ATC	GAC	3216
																	2

				200			
	Phe Glu Gl	y Asp Thr 1060	Leu Val Asn	Arg Ile 0 1065	_	Gly Ile 2 070	Asp
5		u Asp Gly	AAC ATC CTG Asn Ile Leu 1080				
10			TAT ATC ATG Tyr Ile Met 1095				
15		n Phe Lys	ATC CGC CAC Ile Arg His 110	Asn Ile 0		Ser Val	
ı			CAG CAG AAC Gln Gln Asn				
20			CAC TAC CTG His Tyr Leu		Gln Ser Ala		
25		sn Glu Lys	CGC GAT CAC Arg Asp His 1160				
30			CTC GGC ATG Leu Gly Met 1175			TAA	3546
•	(	(2) INFORMA	TION FOR SEC	Q ID NO:13	33:		
35	() ()	A) LENGTH: 3) TYPE: an C) STRANDED	NESS: single	acids			
40	(ii)		TYPE: prote				
45	(xi)	SEQUENCE	DESCRIPTION	: SEQ ID 1	NO:133:		
	Met Asn Al	la Pro Glu 5	Arg Gln Pro	Gln Pro 1	Asp Gly Gly	Asp Ala 15	Pro
	Gly His G	lu Pro Gly 20	Gly Ser Pro	Gln Asp	Glu Leu Asp	Phe Ser	Ile
50	Leu Phe As		Tyr Leu Asn	Pro Asn	Glu Glu Glu 45	Pro Asn	Ala
	His Lys Va 50	al Ala Ser	Pro Pro Ser	Gly Pro	Ala Tyr Pro 60	Asp Asp	Val
55		yr Gly Leu	Lys Pro Tyr			Leu Ser	Gly 80
		ro Gly Arg	Phe Gly Glu	Pro Asp	Arg Val Gly	Pro Gln	Lys

										,						
					85					90					95	
	Phe	Leu	Ser	Ala	Ala	Lys	Pro	Ala	Gly	Ala	Ser	Gly	Leu	Ser	Pro	Ara
				100		-			105			2		110		3
	Ile	Glu	Ile	Thr	Pro	Ser	His	Glu		Ile	Gln	Δla	Val		Pro	T.en
5			115					120			<b></b>		125	Cry	110	Deu
•	Δτα	Met		\ en	A 1 =	@1v	Len		17-1	C1	<b>61</b> -	Dana		<b>7</b>	.1.	<b>~</b> 1
	n.g	130	AL 9	Mah	AIA	СТУ		пеп	val	GIU	GIII		Pro	ьeu	Ala	GIA
	17-1		N1 -		D	<b>3</b>	135	m1	•	_		140				
		Ala	Ala	ser	Pro		Pne	Thr	ren	Pro		Pro	Gly	Phe	Glu	Gly
40	145	_		_		150					155					160
10	Tyr	Arg	Glu	Pro		Сув	Leu	Ser	Pro	Ala	Ser	Ser	Gly	Ser	Ser	Ala
					165					170					175	
	Ser	Phe	Ile	Ser	qaA	Thr	Phe	Ser	Pro	Tyr	Thr	Ser	Pro	Cys	Val	Ser
				180					185					190		
	Pro	Asn	Asn	Gly	Gly	Pro	Asp	Asp	Leu	Cys	Pro	Gln	Phe	Gln	Asn	Ile
15			195					200					205			
	Pro	Ala	His	Tyr	Ser	Pro	Arg	Thr	Ser	Pro	Ile	Met	Ser	Pro	Arq	Thr
		210					215					220			-	
	Ser	Leu	Ala	Glu	qaA	Ser	Cys	Leu	Gly	Arq	His	Ser	Pro	Val	Pro	Ara
	225				-	230	•				235					240
20		Ala	Ser	Ara	Ser		Ser	Pro	Glv	Δla		Δrα	Δτα	Hig	Ser	
				3	245				1	250		3	9		255	Cy B
	Ala	Glu	Ala	Len		Ala	T.em	Pro	Pro			Car	Dro	Gl n		Car
				260				110	265	O <sub>T</sub> y	ALU	Jer	FLO	270	ALG	Ser
	Ara	Ser	Dro		Dro	Gln.	Dro	Cor		ui a	Va 1	77-	Desa		X	***
25	****		275	UCI	110	0111	FIU	280	DCI	птр	VOIT	AIa		GIH	Asp	птв
20	G1	00-	-	27.	<i>a</i> 1	The same	D		77-7		<b>a</b> 1	<b>a</b>	285	**- 3	-1.	
	СТА	Ser	PIO	ATG	GLY	TYE		PIO	vaı	Ala			Ала	vaı	тте	Met
	•	290	-				295		_	_		300				
		Ala	теп	Asn	ser		Ala	Thr	Asp	Ser		Cys	Gly	Ile	Pro	
00	305		_	_		310					315					320
30	гàв	Met	Trp	Lys		Ser	Pro	Asp	Pro	Ser	Pro	Val	Ser	Ala	Ala	Pro
					325					330					335	
	Ser	Lys	Ala	Gly	Leu	Pro	Arg	His	Ile	Tyr	Pro	Ala	Val	Glu	Phe	Leu
				340					345					350		
	Gly	Pro	Cys	Glu	Gln	Gly	Glu	Arg	Arg	Asn	Ser	Ala	Pro	Glu	Ser	Ile
35			355					360					365			
	Leu	Leu	Val	Pro	Pro	Thr	Trp	Pro	Lys	Pro	Leu	Val	Pro	Ala	Ile	Pro
		370					375		_	•		380				
	Ile	Сув	Ser	Ile	Pro	Val	Thr	Ala	Ser	Leu	Pro	Pro	Leu	Glu	Tro	Pro
	385	=				390					395				•	400
40	Leu	Ser	Ser	Gln	Ser	Glv	Ser	Tvr	Glu	Leu		Tle	Glu	Val	Gln	
					405			-3-							415	
	Lvs	Pro	His									Gly	Ser			
				420	3			-1-	425		Ozu	0+1	561	430	Ory	ALU
	Val	Lys	פומ		Thr	@lsz	Gly	TH's			17-1	<i>ر</i> ا ب	T 011		<b>~1</b>	Th ex-
45		-, .	435			CTY	CLY	440	FLU	Val	Val	GIII		пто	GLY	IYI
70	Mot	G111		Lazo	Dro	Lou	<i>α</i> 1		<b>~1</b>	~1 ·	73 h	71.	445	m1		<b>3</b>
	1100	Glu 450	YOU	ny s	FIQ	пец		nea	GIII	TTE	PILE		GIĀ	Thr	Ald	Asp
	<b>63.</b>		T1.	T	T	D	455		<b>-</b> 31	_	<u>.</u> .	460		_		
		Arg	TIG	neu	пув		HIS	Ата	rne	ıyr		vaı	HIS	Arg	тте	
EΛ	465	<b>T</b>	on1		1	470		_	_		475					480
50	GIY	ГÀЗ	unr	vaı		Tnr	Thr	Ser	Tyr		Lys	Ile	Val	Gly		Thr
	_				485					490					495	
	ràs	Val	Leu		Ile	Pro	Leu	Glu		Lys	Asn	Asn	Met	Arg	Ala	Thr
		_	_	500					505					510		
	Ile	Asp		Ala	Gly	Ile	Leu	Lys	Leu	Arg	Asn	Ala	Asp	Ile	Glu	Leu
55			515					520					525			
	Arg	Lys	Gly	Glu	Thr	Asp	Ile	Gly	Arg	Lys	Asn	Thr	Arg	Val	Arg	Leu
									_	-			_		_	

	17n 1	530		4	<b></b> _	~ 7	535				_	540				
	val	Pne	Arg	vaı	HIS		Pro	Glu	Ser	Ser			Ile	Val	Ser	Leu
	545	mı.		_	_	550					555					560
5	GIN	Tnr	АТЯ	ser	Asn 565	Pro	Ile	Glu	Сув	Ser 570	Gln	Arg	Ser	Ala	His 575	Glu
	Leu	Pro	Met	Val 580	Glu	Arg	Gln	qaA	Thr 585	Asp	Ser	Сув	Leu	Val 590	Tyr	Gly
	Gly	Gln			Ile	Leu	Thr		Gln	Asn	Phe	Thr	Ser		Ser	Lys
10	Val	Val	595 Phe	Thr	Glu	Lys	Thr	600 Thr		Gly	Gln	Gln	605 Ile	Trp	Glu	Met
		610					615					620				
	Glu 625	Ala	Thr	Val	Asp	Lys 630	qaA	Lys	Ser	Gln	Pro 635	Asn	Met	Leu	Phe	Val 640
15	Glu	Ile	Pro	Glu	Tyr 645	Arg	Asn	Lys	His	Ile 650	Arg	Thr	Pro	Val	Lys 655	Val
	Asn	Phe	Tyr	Val	Ile	Asn	Gly	Lys	Arg 665		Arg	Ser	Gln	Pro 670		His
	Phe	Thr	Tyr 675		Pro	Val		Ala 680		ГÀв	Thr	Glu			Asp	Glu
20	Tyr	Asp 690		Thr	Leu	Ile	Cys		Pro	Thr	His		685 Gly	Leu	Gly	Ser
			Tyr	Tyr	Pro		695 His	Pro	Met	Val		700 Glu	Ser	Pro	Ser	Сув
	705	17-1	77-	m}	<b>M</b> - 4-	710		_			715			_		720
25					Met 725					730					735	
				740	Arg				745					750		
	Gln	Arg	Ser 755	Lys	Ser	Leu	Ser	Pro 760	Ser	Leu	Leu	Gly	Tyr 765	Gln	Gln	Pro
30	Ala	Leu 770	Met	Ala	Ala	Pro	Leu 775	Ser	Leu	Ala	Asp	Ala 780	His	Arg	Ser	Val
	Leu 785	Val	His	Ala	Gly	Ser 790	Gln	Gly	Gln	Ser	Ser 795	Ala	Leu	Leu	His	Pro 800
35	Ser	Pro	Thr	Asn	Gln 805	Gln	Ala	Ser	Pro	Val 810		His	Tyr	Ser	Pro 815	Thr
	Asn	Gln	Gln	Leu 820	Arg	Cys	Gly	Ser			Glu	Phe	Gln			Met
	Tyr	ayD			Phe	Ala	Pro		825 Thr	Thr	Arg	Pro		830 Pro	Pro	Pro
40	Val	Ser	835 Gln	Gly	Gln	Arg	Leu	840 Ser	Pro	Gly	Ser	Tyr	845 Pro	Thr	Val	Ile
	~1 m	850			<b>-1</b> -											
	865				Ala	870					875					880
45	Val	Ser	Asp	Gln	Lув 885	Glu	Val	Leu	Pro	Ala 890	Gly	Val	Thr	Ile	Lys 895	Gln
	Glu	Gln	Asn	Leu 900	qaA	Gln	Thr	Tyr	Leu 905	Asp	Asp	Val	Asn	Glu 910	Ile	Ile
	Arg	Lys	Glu 915	Phe	Ser	Gly	Pro			Arg	Asn	Gln			Ile	Leu
50	Gln			Val	Pro	Arg		920 Arg	Asp	Pro	Pro		925 Ala	Thr	Met	Val
		<b>Г</b> Ув 930	Gly	Glu	Glu		935 Phe	Thr	Gly	Val		940 Pro	Ile	Leu	Val	
	945	λ	G1	N	77-7	950	<b>a</b> 2.		•	<b>-</b> 1-	955	***	~ -	~-		960
55					Val 965					970					975	
	GLU	GTA	Asp	Ala	Thr	ıyr	Gly	ГÀв	Leu	Thr	Leu	Lys	Phe	Ile	GÀa	Thr

				980					985					990				
	Thr	Gly	Lys 995	Leu	Pro	Val		Trp 000.	Pro	Thr	Leu		Thr 005		Leu	Thr		
5	_	Gly 1010	Val	Gln	Сув		Ser .015	Arg	Tyr	Pro		His .020	Met	Lys	Gln	His		
	Asp 025	Phe	Phe	Lys		Ala 1030	Met	Pro	Glu	_	Tyr .035	Val	Gln	Glu	-	Thr .040		
		Phe	Phe	Lys 1	Asp .045	Asp	Gly	naA	_	Lys .050	Thr	Arg	Ala		Val .055	Lys		
10	Phe	Glu	_	Asp		Leu	Val				Glu	Leu		Gly .070	Ile	Asp		
	Phe	_		Asp	Gly	Asn				His	Lys		Glu .085	Tyr	Asn	Tyr		
15				Asn	Val	-			Ala	Asp		Gln 100	Lys	Asn	Gly	Ile		
			Asn	Phe				His	Asn				Gly	Ser		Gln 120		
		Ala	qaA	His 1			Gln	naA				Gly	Asp					
20	Leu	Leu		Asp		His	Tyr				Gln	Ser				Lys		
	Asp			Glu	Lys	Arg				Val	Leu				Val	Thr		
25				Ile	Thr			Met	Дар									
			(2)	INE	ORM				ם ו	NO:1								
		( -		EQUEN														
30		,-	(A)	LENG	TH:	2802	2 bas	se pa			•							
			(C)	STRA	ANDEI	ONES	S: 8:	ingle	<b>=</b>									
35		<b>(</b> :		MOLEC														
			. :	FEAT														
				NAM LOC				_	eque	ace								
40				OTI														
		(:	ci) :	SEQUI	ENCE	DES	CRIP'	rion	: SE	Q ID	NO:	134:						
45				AAG Lys											_		48	
.0	1	V	-	_,_	5	-				10	7				15			
-				GAC Asp													96	
50	<b>V</b> 444	GIU	Deu	20	ULY	wab		7.014	25	114,5	2,3	1110	501	30		4		
				GGC Gly													144	
55	GIU	GLY	35	-Ly	veħ	VIG	~***	40	OLY	_,,,			45	_,,				
55	TGC	ACC	ACC	GGC	AAG	CTG	ccc	GTG	ccc	TGG	CCC	ACC	CTC	GTG	ACC	ACC	192	269
																		203

									•									
	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr		
5			TAC Tyr														240	
10			GAC Asp														288	
15			ATC Ile														336	
13			TTC Phe 115														384	
20			TTC Phe														432	
25			AAC Asn														480	
30			AAG Lys														528	
٥٣		_	CTC Leu														576	
35			CTG Leu 195														624	
40			GAC Asp										Leu				672	
45		Thr					Thr					Glu				TCC Ser 240	720	
50						Gly					Leu					TAC	768	
					Lys					Arg					Lev	ATC	816	
55	GAC	GAG	CTG	GAG	CTG	GAD	TTG	GAT	CAC	AAG	GAC	GA/	A CTG	; ATC	CAC	AAG	864	270

										_,,							
	Asp	Glu	Leu 275	Glu	Leu	Glu	Leu	Asp 280	Gln	Lys	Asp	Glu	Leu 285	Ile	Gln	Lys	
	CTG	CAG	AAC	GAG	CTG	GAC	AAG	TAC	CGC	TCG	GTG	ATC	CGA	CCA	GCC	ACC	912
5					Leu												7.2
		290				-	295	•				300	3				
										•							
					AAG												960
40		Gln	Ala	Gln	ГÀв		Ser	Ala	Ser	Thr	_	Gln	Gly	Glu	Pro	Arg	
10	305					310					315					320	
	ACC	DAG	CGG	CAG	GCG	ΔTC	TCC	GCC	GNG	CCC	»CC	acc	ישיים	GNC	አጥሮ	CNC	1008
					Ala												1000
		2			325					330					335	<b></b>	
15																	
					GTG												1056
	Asp	Leu	Ser		Val	Thr	Leu	Pro	Phe	Tyr	Pro	Lys	Ser	Pro	Gln	Ser	
				340					345					350			
20	7 7 C	ርልጥ	Cutur	מידא	AAG	ממם	GCate	አጥሮ	مليش	GVG	ידיממ	CAC	challada	አጥር	880	7.7.C	1104
20					Lys												1104
	-,-		355		,-	0.1.0	****	360	1104	ռոբ	Aon	тор	365	MCL	шуз	ABII	
	TTG	GAG	CTG	TCG	CAG	ATC	CAG	GAG	ATT	GTG	GAT	TGT	ATG	TAC	CCG	GTG	1152
25	Leu	Glu	Leu	Ser	Gln	Ile	Gln	Glu	Ile	Val	Asp	Cys	Met	Tyr	Pro	Val	
		370					375					380					
	ana.	mam	ccc	770	CA C	3.00	maa	3.00	3 ma		~~~		a. a	ama		max	1000
					GAC Asp												1200
30	385	TYL	GIY	пуъ	нар	390	сув	TIE	TIE	пåв	395	GIY	Asp	Val	GIY	400	
	200					550					323					100	
	CTG	GTG	TAT	GTC	ATG	GAA	GAT	GGT	AAG	GTŤ	GAA	GTT	ACA	AAA	GAA	GGT	1248
	Leu	Val	Tyr	Val	Met	Glu	Asp	Gly	Lys	Val	Glu	Val	Thr	Lys	Glu	Gly	
					405					410					415		
35																	
					ACC												1296
	val	пЛя	Deu.	420	Thr	Mec	GIÀ	PIO	425	гав	vai	Pne	GIY		ьеп	Ala	
				720					743					430			
40	ATT	CTT	TAC	AAC	TGT	ACC	CGG	ACA	GCG	ACC	GTC	AAG	ACT	CTT	GTA	AAT	1344
	Ile	Leu	Tyr	Asn	Cys	Thr	Arg	Thr	Ala	Thr	Val	Lys	Thr	Leu	Val	Asn	
			435					440					445				
45					GCC												1392
40	Val	450	пеп	пр	Ala	TTE	455	Arg	GŢĦ	Сув	Pne	460	inr	тте	Mec	Met	
		150					*33					400					
	AGG	ACA	GGA	CTC	ATC	AAG	CAT	ACC	GAG	TAT	ATG	GAA	TTT	TTA	AAA	AGC	1440
					Ile												
50	465					470					475					480	
					CAG												1488
	val	PLO	ini	rne	Gln 485	ser	டeu	rro	GIU	490	TTE	neu	ser	тАв	Leu 495	ATG	
55					-103					マブリ					733		
	GAT	GTC	CTT	GAA	GAG	ACC	CAC	TAT	GAA	AAT	GGA	GAA	TAT	ATT	ATC	AGG	1536
										•							

									:	272							
	Asp	Val	Leu	Glu 500	Glu	Thr	His	Tyr	Glu 505	Asn	Gly	Glu	Tyr	Ile 510	Ile	Arg	
5					GGG Gly												1584
10					GAA Glu												1632
					GGA Gly												1680
15					GCA Ala 565												1728
20	_	_			GAC Asp		_				_		_				1776
25					GCA Ala												1824
30					TTC Phe												1872
0.5					GGA Gly												1920
35					GAA Glu 645												1968
40.					GAC Asp												2016
45					GGG Gly												2064
50					AGC Ser											CTA Leu	2112
55		Gly							_			Gly				GAT Asp 720	2160
55	TCT	ACA	ACC	AGA	TTT	TAC	ACA	GCA	TGT	GTG	GTA	. GAA	GCT	TTT	GCC	TAT	2208

										213							
	Ser	Thr	Thr	Arg	Phe 725	Tyr	Thr	Ala	Сув	Val 730	Val	Glu	Ala	Phe	Ala 735	Tyr	
	CTG	CAT	TCC	ааа	GGA	ATC	יזיינים	TAC	AGG	GAC	CTC	AAG	CCA	GAA	a a m	ריזיר	2256
5												Lys					2230
	ATC	CTA	GAT	CAC	CGA	GGT	TAT	GCC	AAA	CTG	GTT	GAT	TTT	GGC	TTT	GCA	2304
10												Asp					
	DAG	272	מדמ	GGA	սեւներ	GGZ	מממ	מממ	מטמ	TCC	ልሮሞ	TTT	ጥርም	aca	אכיתי	CCA	2352
45												Phe 780					2332
15	ara	mam	CITTE	000	CON	CAC	3.000	a mos	ama	220		000	a	a » a	3 000	max.	2400
												GGC Gly					2400
	785	-7-	Vai	AIG	110	790	***	110	Deu	YOU	795	GIY		Nap	116	800	
20	GCC	GAC	TAC	TGG	TCA	CTG	GGA	ATC	CTA	ATG	TAT	GAA	CTC	CTG	ACT	GGC	2448
	Ala	Asp	Tyr	Trp	Ser 805	Leu	Gly	Ile	Leu	Met 810	Tyr	Glu	Leu	Leu	Thr 815	Gly	
	AGC	CCA	CCT	TTC	TCA	GGC	CCA	GAT	CCT	ATG	AAA	ACC	TAT	AAC	ATC	ATA	2496
25	Ser	Pro	Pro	Phe 820	Ser	Gly	Pro	Asp	Pro 825	Met	Lys	Thr	Tyr	Asn 830	Ile	Ile	
	TTG	AGG	GGG	ATT	GAC	ATG	ATA	GAA	TTT	CCA	AAG	AAG	ATT	GCC	AAA	AAT	2544
30												ГÀв					
	GCT	GCT	AAT	TTA	ATT	AAA	AAA	CTA	TGC	AGG	GAC	AAT	CCA	TCA	GAA	AGA	2592
												Asn 860					
35																	
												CAA					2640
	865	GLY	ASII	neu	пуз	870	GIY	val	гуя	ABD	875	Gln	пув	urs	ъyв	880	
40	TTT	GAG	GGC	TTT	AAC	TGG	GAA	GGC	TTA	AGA	AAA	GGT	ACC	TTG	ACA	CCT	2688
	Phe	Glu	Gly	Phe	Asn 885	Trp	Glu	Gly	Leu	Arg 890	Lys	Gly	Thr	Leu	Thr 895	Pro	
	CCT	ATA	ATA	CCA	AGT	GTT	GCA	TCA	CCC	ACA	GAC	ACA	AGT	AAT	TTT	GAC	2736
45	Pro	Ile	Ile	Pro 900	Ser	Val	Ala	Ser	Pro 905	Thr	Asp	Thr	Ser	Asn 910	Phe	Asp	
	AGT	TTC	CCT	GAG	GAC	AAC	GAT	GAA	CCA	CCA	CCT	GAT	GAC	AAC	TCA	GGA	2784
50	Ser	Phe	Pro 915	Glu	Asp	Asn	Asp	Glu 920	Pro	Pro	Pro	Asp	Авр 925	Asn	Ser	Gly	
	TGG	GAT	ATA	GAC	TTC	TAA											2802
					Phe												
	•	930	_	•													
55																	

274

## (2) INFORMATION FOR SEQ ID NO:135:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 933 amino acids
- (B) TYPE: amino acid

5

55

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- 10 (v) FRAGMENT TYPE: internal
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

		()	CI) a	seQue	MCE	שמע	.KIF1	LON	SE(	עב ג	NO:1	.35:				
15	1	Val		_	5					10					15	
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	ГÀв	Phe	Ile
20	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
	65	Thr				70					75					80
<b>25</b>		His	_		85	_				90					95	
		Thr		100					105					110		
		Lys	115					120					125			
30		Asp 130					135					140				
	145	Tyr				150					155					160
35	_	Ile	_		165					170					175	
		Gln		180					185					190		
		Val	195					200					205			
40		Lys 210					215		•			220				
	225	Thr				230					235					240
45	_	Leu	_		245					250					255	
		Leu		260					265					270		
	_	Glu	275					280					285			
50		Gln 290					295					300				
	Gln 305	Gln	Ala	Gln	Lys	Gln 310		Ala	Ser	Thr	Leu 315		Gly	Glu	Pro	320

274

Thr Lys Arg Gln Ala Ile Ser Ala Glu Pro Thr Ala Phe Asp Ile Gln

Asp Leu Ser His Val Thr Leu Pro Phe Tyr Pro Lys Ser Pro Gln Ser

325

				240					245							
	Tarm	2	T 011	340	+	<b>61.</b>	77.	T1_	345		<b>.</b>	<b>3</b>	D1	350	•	•
	пув	Ash	Leu 355	тте	тув	GIU	ALA	360	ьеп	Asp	Asn	Asp		Mec	гув	Asn
	Low	Glu.		Co	01n	Tla	<b>~1</b> -		т1 -	77 n 7	B	<b>~</b>	365	ML	D	**- 7
5	пеп	370	Leu	Ser	GIII	TIC	375	GIU	TIE	val	Asp	380	Met	TÄL	PIO	var
Ū	Glu		Gly	T.v.d	λαη	Ser		T10	тЪ	Lare	G1.,		λαn	v-1	G1	Co*
	385	- / -	OLY	Буб	тор	390	Cys	116	116	uya	395	GIY	тор	val	GLY	400
		Val	Tyr	Va1	Met		Agn	Glv	Lare	V=1		Val	Thr	Tare	Glu	
			-1-		405			O.L.y	, -	410	014	141	1111	<b>1</b> 375	415	GIY
10	Val	Lvs	Leu	Cvs		Met.	Glv	Pro	Glv		Val	Phe	Glv	Glu		Δla
		-2		420			1		425	-12			,	430		
	Ile	Leu	Tyr		Cys	Thr	Arq	Thr		Thr	Val	Lvs	Thr		Val	Asn
			435		•		_	440					445			
	Val	Lys	Leu	Trp	Ala	Ile	Asp	Arg	Gln	Cys	Phe	Gln	Thr	Ile	Met	Met
15		450					455	_		_		460				
	Arg	Thr	Gly	Leu	Ile	Lys	His	Thr	Glu	Tyr	Met	Glu	Phe	Leu	Lys	Ser
•	465					470					475					480
	Val	Pro	Thr	Phe	Gln	Ser	Leu	Pro	Glu	Glu	Ile	Leu	Ser	Lys	Leu	Ala
					485					490					495	
20	Asp	Val	Leu		Glu	Thr	His	Tyr		Asn	Gly	Glu	Tyr	Ile	Ile	Arg
				500		_			505					510		
	GIn	GTA	Ala	Arg	GIY	Asp	Thr		Phe	Ile	Ile	Ser	-	Gly	Thr	Val
	•	TY_ 7	515	•	a1	•		520	~ -	~ 7			525	_,		
25	Asn		Thr	Arg	GIU	Asp		Pro	ser	GIU	Asp		vaı	Phe	Leu	Arg
20	The	530	C11.	T	C1	7	535	Db	<b>~</b> 3	<b>~</b> 1	*	540	T	<b>01</b> -	<b>~</b> 1	<b>a</b> 1
	545	пеп	Gly	пув	GIY	550	тгр	Pne	GIĀ	GIU	ьув 555	AIA	Leu	GII	GIY	560
		Val	Arg	Thr	Δla		Val	716	212	Δla		λla	บอไ	Thr	Cve	
					565		***		,,,,,	570	010	ALU	<b>V</b> 41		575	cu
30	Val	Ile	Asp	Arq		Ser	Phe	Lvs	His		Ile	Glv	Glv	Leu		Asp
			•	580	1			-4-	585			1	1	590		
	Val	Ser	Asn	Lys	Ala	Tyr	Glu	qsA	Ala	Glu	Ala	Lys	Ala	Lys	Tyr	Glu
			595	-		_		600				•	605	-	•	
	Ala	$\operatorname{Glu}$	Ala	Ala	Phe	Phe	Ala	Asn	Leu	Lys	Leu	Ser	Asp	Phe	Asn	Ile
35		610					615			•		620				
	Ile	Asp	Thr	Leu	Gly	Val	Gly	Gly	Phe	Gly	Arg	Val	Glu	Leu	Val	Gln
	625					630					635					640
	Leu	ГЛЯ	Ser	Glu	Glu	Ser	Гув	Thr	Phe	Ala	Met	Lys	Ile	Leu	Lys	ГÀв
40					645	_			-	650					655	
40	Arg	His	Ile		Asp	Thr	Arg	Gln					Arg		Glu	Lys
	<b>41</b> -	<b>-</b> 1-	<b>V-</b> -	660	<b>~</b> 1								_	670		
	GIII	TTE		GIN	GIY	Ата	HIS		Asp	Pne	TTE	vaı		ren	Tyr	Arg
	Th.~	Dha	675	7 cm	Cor	T	The same	680	The same	Mot	7	Ma+	685	77-	O	Tou
45	1414	690	шув	Asp	261	пуs	695	ПСП	TAT	Mec	пеп	700	GIU	мта	Сув	Leu
1.0	Glv		Glu	T.en	Trn	Thr		T.e.ii	Δνα	Aan	λνα		Ser	Dhe	Glu	Авр
	705	<b>-</b>	014	200	ııp	710	110	neu	nrg	nop	715	GLY	Der	7110	Ozu	720
		Thr	Thr	Ara	Phe		Thr	Ala	Cvs	Va 1		Glu	Ala	Phe	Ala	
				5	725	-1-			-1-	730			•		735	-1-
50	Leu	His	Ser	Lys	Gly	Ile	Ile	Tyr	Arg		Leu	Lys	Pro	Glu	Asn	Leu
				740	_			-	745	-		-		750		
	Ile	Leu	Asp	His	Arg	Gly	Tyr	Ala	Lys	Leu	Val	Asp	Phe	Gly	Phe	Ala
			755					760					765			
	Lys		Ile	Gly	Phe	Gly	Гув	Lys	Thr	Trp	Thr		Сув	Gly	Thr	Pro
55		770	_	_			775					780	_			
	Glu	Tyr	Val	Ala	Pro	Glu	Ile	Ile	Leu	Asn	Lys	Gly	His	Asp	Ile	Ser

	785					790					795					800	•
	Ala	Asp	Tyr	Trp	Ser 805	Leu	Gly	Ile	Leu	Met 810	Tyr	Glu	Leu	Leu	Thr 815	Gly	
5	Ser	Pro	Pro	Phe 820	Ser	Gly	Pro	Asp	Pro 825	Met	Lys	Thr	Tyr	Asn 830	Ile	Ile	
	Leu	Arg	Gly 835	Ile	Asp	Met	Ile	Glu 840	Phe	Pro	Lys	Lys	Ile 845	Ala	Lys	Asn	
	Ala	Ala 850	Asn	Leu	Ile	Lys	Lys 855	Leu	Сув	Arg	Asp	Asn 860	Pro	Ser	Glu	Arg	
10	865	Gly				870					875					880	
	Phe	Glu	Gly	Phe	Asn 885	Trp	Glu	Gly	Leu	Arg 890	Lys	Gly	Thr	Leu	Thr 895	Pro	
15		Ile		900					905		_			910			
	Ser	Phe	Pro 915	Glu	Ąsp	Asn	Asp	Glu 920	Pro	Pro	Pro	Asp	Авр 925	Asn	Ser	Gly	
	Trp	<b>qaA</b> 080	Ile	Asp	Phe												
20			(2)	INE	FORM	TION	v FOI	R SEC	OID	NO:1	136:						
25		<b>(</b> )	(A) (B) (C)	EQUEN LENC TYPI STRA	ETH: E: nu ANDEI	2799 iclei ONESS	bas lc ac	se pa cid ingle	airs								
30				OLEC FEATU		TYPI	E: Cl	ANC	÷								
35		,	(B) (D)	NAM LOC	EATIC	ON: :	RMAT	2795 ION:									
				EQUI						•						a. a	40
40		GGC															48
45		CTG Leu															96
		CAG Gln															144
50		CGC Arg 50															192
55		AGC Ser															240

		GAG Glu															28	88
5					85					90					95			
•		TTC															33	36
	Pro	Phe	Tyr	Pro 100	Lys	Ser	Pro	Gln	Ser 105	Lys	Asp	Leu	Ile	Lys 110	Glu	Ala		
10		CTT															38	84
	iie	Leu	115	ASI	Asp	Pne	Met	цув 120	ASI	Leu.	GIU	ren	125	Gin	ile	GIN		
15		ATT															4:	32
15	GIU	11e 130	Val	Asp	Cys	Met	135	PIO	vai	GIU	Tyr	140	гуs	Asp	ser	Cys		
		ATC															41	80
20	145	Ile	nys	Gru	GIĄ	150	Val	GIY	ser	Leu	155	Tyr	vai	Met	GIU	160		
		AAG															52	28
	сту	Lys	VAI	GTU	165	IIII	гув	GIU	GIY	170	гÀв	Leu	Cys	Thr	175	GIÀ		
25	CC3	CO.		ama	man)	000	<b></b>	mma	aam	3 Otros	-							
		GGA Gly															5	76
			_	180		_			185			•		190		J		
30		GCG															6:	24
	Thr	Ala	Thr 195	Val	ГÀв	Thr	Leu	Val 200	Asn	Val	Ъуs	Leu	Trp 205	Ala	Ile	Asp		
35		CAA															6	72
33	Arg	Gln 210	cys	Pne	GIN	ınr	215	Met	Met	Arg	Thr	220 GLY	Leu	TTE	гÀг	HIS		
		GAG															7:	20
40	225	Glu	ıyı	Met	GIU	230	Leu	тАв	ser	vaı	235	ınr	Pne	GII	ser	240		
		GAA															7	68
45		Glu	GIU	116	245	261	рув	ьец	Ala	250	Val	neu	GIU	GIU	255	UIB		
70	TAT	GAA	AAT	GGA	GAA	TAT	ATT	ATC	AGG	CAA	GGT	GCA	AGA	GGG	GAC	ACC	В	16
		Glu																
50		TTT															8	64
	Phe	Phe	11e 275	Ile	Ser	ГÀЗ	Gly	Thr 280	Val	Asn	Val	Thr	Arg 285	Glu	Asp	Ser		
		AGT															9	12
55	Pro	Ser 290	Glu	Asp	Pro	Val	Phe 295	Leu	Arg	Thr	Leu	Gly 300	Lys	Gly	qaA	Trp		

278 ·

		•							•								
	TTT	GGA	GAG	AAA	GCC	TTG	CAG	GGG	GAA	GAT	GTG	AGA	ACA	GCA	AAC	GTA	960
	Phe	Gly	Glu	Lys	Ala	Leu	Gln	Gly	Glu	Asp	Val	Arg	Thr	Ala	Asn	Val	
	305					310					315					320	
5																	
						GTA											1008
	Ile	Ala	Ala	Glu	_	Val	Thr	Сув	Leu		Ile	Asp	Arg	Asp		Phe	
•					325					330					335		
40																	
10						GGG											1056
	гув	HIB	Leu	340	GIY	Gly	ьеи	двр	-	vaı	ser	Asn	гув		Tyr	GIU	
				340					345					350			
	TAD	GCA	AAD	GCT	ааа	GCA	ααα	יייביי	aan	ርርጥ	aan	GCG	GCT	ттс	That	GCC	1104
15						Ala											1101
			355		-,-		_,_	360					365				
	AAC	CTG	AAG	CTG	TCT	GAT	TTC	AAC	ATC	ATT	GAT	ACC	CTT	GGA	GTT	GGA	1152
	Asn	Leu	Lys	Leu	Ser	Asp	Phe	Asn	Ile	Ile	Авр	Thr	Leu	Gly	Val	Gly	
20		370					375					380					
						GAA											1200
	-	Phe	Gly	Arg	Val	Glu	Leu	Val	Gln		_	Ser	Glu	Glu	Ser	-	
05	385					390					395					400	
25	200	mmm	aan	3 77 77		3 17277				aam	<b>63.6</b>	3 mm	ama	~~~	3.03	202	1040
						ATT											1248
	1111	PHE	AId	MEL	405	Ile	пеп	гуя	пля	410	uta	TTE	var	ивр	415	AIG	
					203					410					413		
30	CAG	CAG	GAG	CAC	ATC	CGC	TCA	GAG	AAG	CAG	ATC	ATG	CAG	GGG	GCT	CAT	1296
						Arg											
				420		_			425					430			
	TCC	GAT	TTC	ATA	GTG	AGA	CTG	TAC	AGA	ACA	TTT	AAG	GAC	AGC	AAA	TAT	1344
35	Ser	Asp	Phe	Ile	Val	Arg	Leu	Tyr	Arg	Thr	Phe	Lys	qeA	Ser	Lys	Tyr	
			435					440					445				
						GAA											1392
40	Leu	-	Met	Leu	Met	Glu		Сув	Leu	Gly	GIA		Leu	Trp	Thr	IIe	
40		450					455					460					
	СТС	λGG	CAT	מטמ	GGT	TCG	ملحلجلة	GNA	CAT	ייים אי	מימ	אכיכי	D C D	ششك	ጥልሮ	ACA	1440
						Ser											1110
	465		p	9	<b></b> 1	470		014	TOP		475	****	9	1 110	-,-	480	
45											`						
	GCA	TGT	GTG	GTA	GAA	GCT	TTT	GCC	TAT	CTG	CAT	TCC	AAA	GGA	ATC	ATT	1488
	Ala	Сув	Val	Val	Glu	Ala	Phe	Ala	Tyr	Leu	His	Ser	Lys	Gly	Ile	Ile	
					485					490			_		495		
											•						
50						CCA											1536
	Tyr	Arg	qaA	Leu	Lys	Pro	Glu	Asn	Leu	Ile	Leu	Asp	His	Arg	Gly	Tyr	
				500					505	•				510			
re						TTT											1584
55	Ala	гÀв		val	Asp	Phe	gry		АТЯ	nys	тЛа	тте	_	rne	GTĀ	ьув	
			515					520					525				

5	ACA Thr 530								1632
	CTG Leu								1680
10	CTA Leu								1728
15	CCT Pro		_						1776
20	TTT Phe								1824
25	TGC Cys 610								1872
	AAA Lys							Trp	1920
30	TTA Leu								1968
35	CCC Pro								2016
40	CCA Pro								2064
45	CCG Pro 690				 	 	 	 	 2112
	GTG Val								2160
50	AGC Ser								2208
55	CTG Leu								2256

280

		GTG Val 755													2304
5		CAC His													2352
10		GTC Val		Glu											2400
15		CGC Arg													2448
20		CTG Leu													2496
25		CTG Leu 835										_		_	2544
23	 	CAG Gln											-		2592
30		GAC Asp							•						2640
35		GGC Gly													2688
40		TCC Ser											_		2736
45		CTG Leu 915													2784
45		TAC Tyr		GTAA											2799
50		(2	) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	137:					
	(	i) S (A)	EQUE LEN								•	•			

280

(B) TYPE: amino acid

(C) STRANDEDNESS: single

281

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

5 (xi) SEQUENCE DESCRIPTION: SEO ID NO:137:

Met Gly Thr Leu Arg Asp Leu Gln Tyr Ala Leu Gln Glu Lys Ile Glu 10 10 Glu Leu Arg Gln Arg Asp Ala Leu Ile Asp Glu Leu Glu Leu Glu Leu 25 Asp Gln Lys Asp Glu Leu Ile Gln Lys Leu Gln Asn Glu Leu Asp Lys 40 Tyr Arg Ser Val Ile Arg Pro Ala Thr Gln Gln Ala Gln Lys Gln Ser 15 55 Ala Ser Thr Leu Gln Gly Glu Pro Arg Thr Lys Arg Gln Ala Ile Ser 70 75 Ala Glu Pro Thr Ala Phe Asp Ile Gln Asp Leu Ser His Val Thr Leu 90 20 Pro Phe Tyr Pro Lys Ser Pro Gln Ser Lys Asp Leu Ile Lys Glu Ala 105 Ile Leu Asp Asn Asp Phe Met Lys Asn Leu Glu Leu Ser Gln Ile Gln 120 Glu Ile Val Asp Cys Met Tyr Pro Val Glu Tyr Gly Lys Asp Ser Cys 25 135 140 Ile Ile Lys Glu Gly Asp Val Gly Ser Leu Val Tyr Val Met Glu Asp 150 155 Gly Lys Val Glu Val Thr Lys Glu Gly Val Lys Leu Cys Thr Met Gly 170 30 Pro Gly Lys Val Phe Gly Glu Leu Ala Ile Leu Tyr Asn Cys Thr Arg 185 Thr Ala Thr Val Lys Thr Leu Val Asn Val Lys Leu Trp Ala Ile Asp 200 Arg Gln Cys Phe Gln Thr Ile Met Met Arg Thr Gly Leu Ile Lys His 35 215 220 Thr Glu Tyr Met Glu Phe Leu Lys Ser Val Pro Thr Phe Gln Ser Leu 235 Pro Glu Glu Ile Leu Ser Lys Leu Ala Asp Val Leu Glu Glu Thr His 245 250 40 Tyr Glu Asn Gly Glu Tyr Ile Ile Arg Gln Gly Ala Arg Gly Asp Thr 265 Phe Phe Ile Ile Ser Lys Gly Thr Val Asn Val Thr Arg Glu Asp Ser 280 Pro Ser Glu Asp Pro Val Phe Leu Arg Thr Leu Gly Lys Gly Asp Trp 45 295 Phe Gly Glu Lys Ala Leu Gln Gly Glu Asp Val Arg Thr Ala Asn Val 310 315 Ile Ala Ala Glu Ala Val Thr Cys Leu Val Ile Asp Arg Asp Ser Phe 330 50 Lys His Leu Ile Gly Gly Leu Asp Asp Val Ser Asn Lys Ala Tyr Glu 345 Asp Ala Glu Ala Lys Ala Lys Tyr Glu Ala Glu Ala Ala Phe Phe Ala 360 Asn Leu Lys Leu Ser Asp Phe Asn Ile Ile Asp Thr Leu Gly Val Gly 55 375 380 Gly Phe Gly Arg Val Glu Leu Val Gln Leu Lys Ser Glu Glu Ser Lys

									•	202						
	385					390					395					400
	Thr	Phe	Ala	Met	Lys 405	Ile	Leu	Lys	Lys	Arg 410	His	Ile	Val	Asp	Thr 415	Arg
5	Gln	Gln	Glu	His 420	Ile	Arg	Ser	Glu	Lys 425	Gln	Ile	Met	Gln	Gly 430	Ala	His
	Ser	Asp	Phe 435	Ile	Val	Arg	Leu	Tyr 440	Arg	Thr	Phe	Lys	Asp 445	Ser	rya	Tyr
	Leu	Tyr 450	Met	Leu	Met	Glu	Ala 455	Cys	Leu	Gly	Gly	Glu 460	Leu	Trp	Thr	Ile
10	Leu 465	Arg	Asp	Arg	Gly	Ser 470	Phe	Glu	Asp	Ser	Thr 475	Thr	Arg	Phe	Tyr	Thr 480
	Ala	Сув	Val	Val	Glu 485	Ala	Phe	Ala	Tyr	Leu 490	His	Ser	Lys	Gly	Ile 495	Ile
15	Tyr	Arg	Asp	Leu 500	ГÀЗ	Pro	Glu	Asn	Leu 505	Ile	Leu	Asp	His	Arg 510	Gly	Tyr
	Ala	Lys	Leu 515	Val	Asp	Phe	Gly	Phe 520	Ala	Lys	ГЛЯ	Ile	Gly 525	Phe	Gly	Lys
		530	_			-	535				-	540		Pro		
20	545					550					555		_	Ser		560
					565				_	570				Ser	575	
25				580					585					Asp 590		
			595					600					605	Ile		
00		610					615					620		Lys		
30	625					630					635			Asn		640
	•				645					650				Ser	655	
35				660					665					Asp 670		_
			675					680					685	Phe		
40		690					695					700		Phe		
40	705					710					715			Gly		720
					725					730				Gly	735	
45				740					745					Pro 750 Ser		
			755					760					765	Met		
50		770					775					780				
50	785					790					795			Gly		800
					805					810				Val Ile	815	
55				820					825					830 Ile		
		-1-					-1-						-1-			

											-							
•			835					840					845					
	qaA	Lys 850	Gln	ГÀв	Asn	Gly	Ile 855	Lys	Val	Asn	Phe	860 Lys	Ile	Arg	His	Asn		
_	Ile	Glu	Asp	Gly	Ser	Val	Gln	Leu	Ala	qaA		Tyr	Gln	Gln	Asn			
5	865			_		870		_	_		875	•	•• · _	m	•	880		
	Pro	Ile	GTA	Asp	885	Pro	Val	Leu	Leu	890	qaA	Asn	HIS	Tyr	ьец 895	ser		
	Thr	Gln	Ser	Ala 900	Leu	Ser	ГÀЗ	Asp	Pro 905		Glu	ГÀЗ	Arg	Asp 910	His	Met		
10	Val	Leu	Leu 915	Glu	Phe	Val	Thr	Ala 920	Ala	Gly	Ile	Thr	Leu 925	Gly	Met	Asp		
,	Glu	Leu 930	Tyr	Lys														
15			(2)	IN	FORM	TION	I. FOI	R SEÇ	] ID	NO: 1	.38:							
		£)	(A)	LENC	TH:	2184	l bas	se pa										
20			(C)	TYPE STRA	ANDEI	ONES	ន: នៈ	ingle	÷									
				OLEC FEAT		TYPI	E: cl	ANC										
25				NAM					eque	ice								
				OTI					,									
30		()	xi) s	SEQUI	ENCE	DES	CRIP'	rion	: SE	Q ID	NO:	138:						
				AAG													48	
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu		Thr 10	Gly	Val	Val	Pro	11e 15	Leu		
35	GTC	GAG	СТС	GAC	GGC	GAC	GTA	AAC	GGC	CAC	AAG	TTC:	AGC	GTG	TCC	GGC	96	
				Asp 20												•		
40	GPG	GGC	GAG	GGC	CAT	GCC	ACC	ሞልሮ	GGC	AAG	CTG	ΔCC	רידוכז	DAG	ጥጥር	ATC	144	
40				Gly														
			35					40					45					
	TGC	ACC	ACC	GGC	AAG	CTG	CCC	GTG	CCC	TGG	CCC	ACC	CTC	GTG	ACC	ACC	192	
45	Сув	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr		
				GGC													240	
50	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Сув	Phe	Ser	Arg	Тут 75	Pro	qeA	His	Met	80 Tàs		
	CAG	CAC	GAC	TTC	TTC	AAG	TCC	GCC	ATG	ccc	GAA	GGC	TAC	GTC	CAG	GAG	288	
					Phe					Pro					Gln	Glu		
55					85					90					95			
	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	. AAC	TAC	AAC	ACC	CGC	GCC	GAG	336	283
																		200

										284							
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu	
	GTG	AAG	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAĊ	CGC	ATC	GAG	СТС	DAG	פפר	384
5	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	Lys	Gly	504
	ATC	GAC	TTC	AAG	GAG	GAC	GGÇ	AAC	ATC	CTG	GGG	CAC	AAG	CTG	GAG	TAC	432
10	Ile	Asp 130	Phe	Lys	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr	
	AAC	TAC	AAC	AGC	CAC	AAC	GTC	ጥልጥ	איזיכי	እጥር	acc	GAC	አክር	CNG	820	አክሮ	480
	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	Asp	Lvs	Gln	Lvs	Asn	200
	145					150		•			155					160	
15																	
			AAG														528
	GIÀ	11e	Lys	Val	Asn 165	Phe	гуя	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser	
20	GTG	CAG	CTC	GCC	GAC	CAC	TAC	CAG	CAG	AAC	ACC	ccc	ATC	GGC	GAC	GGC	576
			Leu														• • • • • • • • • • • • • • • • • • • •
				180					185					190			
			CTG														624
25	Pro	Val	Leu	Leu	Pro	Asp	Asn		Tyr	Leu	Ser	Thr		Ser	Ala	Leu	
			195					200					205				
-	AGC	AAA	GAC	ccc	AAC	GAG	AAG	CGC	CAT	ראכי	ΔTC	GTC	היוהים	ריזיכי	CNG	יייירי	672
	Ser	Lys	Asp	Pro	Asn	Glu	Lys	Arq	Asp	His	Met	Val	Leu	Leu	Glu	Phe	072
30		210	_				215					220					
	GTG	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	ATG	GAC	GAG	CTG	TAC	AAG	TCC	720
	Val	Thr	Ala	Ala	Gly	Ile	Thr	Leu	Gly	Met	Asp	Glu	Leu	Tyr	Lys	Ser	
25	225					230					235					240	
35	CCI	CTC	מכיא	m com	CCA	000	3.00	300	200	<i>a</i> . <i>a</i>	ama						
			AGA Arg														768
	1	<del></del>	5		245	1				250	***	nια	110	Val	255	GIU	
40	GGT	TGG	CTG	CAC	AAA	CGA	GGG	GAG	TAC	ATC	AAG	ACC	TGG	CGG	CCA	CGC	816
	GTÀ	Trp	Leu		Lys	Arg	Gly	Glu		Ile	ГÀв	Thr	Trp		Pro	Arg	
				260					265					270			
	TAC	TTC	CTC	CTC	AAG	ААТ	GAT	GGC	ACC	TTC	ATT	GGC	TAC	DAG	GAG	CGG	864
45	Tyr	Phe	Leu	Leu	Lys	Asn	Asp	Gly	Thr	Phe	Ile	Gly	Tyr	Lys	Glu	Arg	
			275				_	280				•	285	•		_	
			GAT														912
50	PLO	290	Asp	val	web	GII	Arg 295	GIU	ATA	LLO	гел	Asn 300	Asn	rne	ser	val	
							~					500					
	GCG	CAG	TGC	CAG	CTG	ATG	AAG	ACG	GAG	CGG	CCC	CGG	ccc	AAC	ACC	TTC	960
		Gln	Сув	Gln	Leu		Lys	Thr	Glu	Arg	Pro	Arg	Pro	Asn	Thr	Phe	
EE	305					310					315					320	
55	איירי	איזיר	CGC	TGC	בידים	ርልሮ	TCC	אכיכי	ארייי	מיזירי	እጥር	CAA	מממ	n.c.c	The state of	ር አጥ	1008
					-10	CAG	190	ALL	AC1	410	ALC	UMA,	CGC	MLC	110	CAL	1008

285

									•	200							
	Ile	Ile	Arg	Cys	Leu 325	Gln	Trp	Thr	Thr	Val 330	Ile	Glu	Arg	Thr	Phe 335	His ·	
5												ACC Thr					1056
10												GAG Glu					1104
45												GAG Glu 380					1152
15												GAG Glu					1200
20												ATC Ile				_	1248
25										Lys		CTC Leu					1296
30												ACC Thr					1344
35												CTG Leu 460					1392
00												TAC Tyr					1440
40												TTC Phe					1488
45					Gly					Ser		CTG Leu					1536
50				Asn					Asp			CTG Leu		Asn			1584
55			Lys					Lys					Gly			Lys	1632
00	GAG	GGG	ATC	AAG	GAC	GGT	GCC	ACC	ATO	AAC	ACC	TTI	TGC	GGC	ACA	CCT	1680

286

	Glu 545	Gly	Ile	Lys	Asp	Gly 550	Ala	Thr	Met	Lys	Thr 555	Phe	Сув	Gly	Thr	Pro 560	
	GAG	TAC	CTG	GCC	CCC	GAG	GTG	CTG	GAG	GAC	AAT	GAC	TAC	GGC	CGT	GCA	1728
5	Glu	Tyr	Leu	Ala	Pro 565	Glu	Val	Leu	Glu	Asp. 570	Asn	Asp	Tyr	Gly	Arg 575	Ala	
				TGG													1776
10	vaı	Asp	rrp	Trp 580	GIY	Leu	GIY	vaı	585	met	ıyr	GIU	Mec	Met 590	Сув	GIÀ	
				TTC Phe													1824
15			595		•			600			•		605				
15				GAG													1872
	Leu	610	GIU	Glu	TTE	Arg	615	PTO	Arg	Thr	Leu	620	PIO	GIU	Ala	гÀв	
20				TCA	-		_									_	1920
	625	Leu	Leu	Ser	GTÀ	630	теп	гув	гув	жър	635	пув	GIII	Arg	Deu	640	
25				GAG Glu													1968
2.0	GLY	Gly	BCI	GIU	645	AIG	шya	GIU		650	GIII	1113	AL 9	rnc	655	7120	
				TGG Trp												_	2016
30	U1,		, ,	660	<b></b>	,,,,,		-7-	665		,			670			
				GTC Val												_	2064
0.5	2,3	110	675		****	552		680			9	-1-	685				
35	TTC	ACG	GCC	CAG	ATG	ATC	ACC	ATC	ACA	CCA	CCT	GAC	CAA	GAT	GAC	AGC	2112
	Phe	Thr 690	Ala	Gln	Met	Ile	Thr 695	Ile	Thr	Pro	Pro	Asp 700	Gln	Asp	Asp	Ser	
40																TCC	2160
	Met 705		Сув	Val	Asp	5er 710		Arg	Arg	Pro	715		Pro	GIN	Pne	Ser 720	
45				AGC Ser													2184
40	ıyı	ser	Ala	. ser	725		AId										
			(2	) IN	FORM	ATIO	N FO	R SE	Q II	NO:	139:						
50		(	i) S	EQUE	NCE	CHAR	ACTE	RIST	:ICS								
			,	LEN TYP					cide	3							
			(C)	STR	ANDE	DNES	S: 8	ingl	.e								
55			(D)	TOP	OLOG	Y: 1	inea	ır									

287

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

5 Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 10 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 15 70 75 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 20 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 135 140 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 25 150 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 170 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 30 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 215 220 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 35 230 235 Gly Leu Arg Ser Arg Gly Thr Met Ser Asp Val Ala Ile Val Lys Glu 250 Gly Trp Leu His Lys Arg Gly Glu Tyr Ile Lys Thr Trp Arg Pro Arg 265 40 Tyr Phe Leu Leu Lys Asn Asp Gly Thr Phe Ile Gly Tyr Lys Glu Arg 280 Pro Gln Asp Val Asp Gln Arg Glu Ala Pro Leu Asn Asn Phe Ser Val 295 . 300 Ala Gln Cys Gln Leu Met Lys Thr Glu Arg Pro Arg Pro Asn Thr Phe 45 Ile Ile Arg Cys Leu Gln Trp Thr Thr Val Ile Glu Arg Thr Phe His 330 Val Glu Thr Pro Glu Glu Arg Glu Glu Trp Thr Thr Ala Ile Gln Thr 345 50 Val Ala Asp Gly Leu Lys Lys Gln Glu Glu Glu Glu Met Asp Phe Arg 360 Ser Gly Ser Pro Ser Asp Asn Ser Gly Ala Glu Glu Met Glu Val Ser 375 380 Leu Ala Lys Pro Lys His Arg Val Thr Met Asn Glu Phe Glu Tyr Leu 55 395 390 Lys Leu Leu Gly Lys Gly Thr Phe Gly Lys Val Ile Leu Val Lys Glu

288

										288						
					405					410					415	
•	Lys	Ala	Thr	Gly 420	Arg	Tyr	Tyr	Ala	Met 425	Lys	Ile	Leu	Lys	Lys 430	Glu	Val
_	Ile	Val			Asp	Glu	Val			Thr	Leu	Thr		Asn	Arg	Val
5	_		435		_	•	_	440	_				445	_	_	
	Leu	GIN 450	Asn	Ser	Arg	His	Pro 455	Phe	Leu	Thr	Ala	Leu 460	Lys	Tyr	Ser	Phe
	Gln	Thr	His	Asp	Arg	Leu	Сув	Phe	Val	Met	Glu	Tyr	Ala	Asn	Gly	Gly
	465					470					475					480
10	Glu	Leu	Phe	Phe	His 485	Leu	Ser	Arg	Glu	Arg 490	Val	Phe	Ser	Glu	Asp 495	Arg
•	Ala	Arg	Phe	Tyr 500	Gly	Ala	Glu	Ile	Val 505	Ser	Ala	Leu	Asp	Tyr 510	Leu	His
15	Ser	Glu	Lys 515	Asn	Val	Val	Tyr	Arg 520	Asp	Leu	Lys	Leu	Glu 525	Asn	Leu	Met
	Leu	Asp 530	Lys	Asp	Gly	His	Ile 535	Lys	Ile	Thr	Asp	Phe 540	Gly	Leu	Сув	Lys
	Glu	Glv	Ile	Lvs	авъ	Glv	Ala	Thr	Met	Lvs	Thr	Phe	Cvs	Gly	Thr	Pro
	545	•		•	•	550				-	555		•	•		560
20	Glu	Tvr	Leu	Ala	Pro	Glu	Val	Leu	Glu	Asp	Asn	Asp	Tvr	Gly	Ara	Ala
					565					570	•		-4 -	4	575	
	Val	Asp	Trp	Trp	Gly	Leu	Gly	Val	Val	Met	Tyr	Glu	Met	Met	Сув	Gly
				580					585		-4			590		
	Arq	Leu	Pro	Phe	Tyr	Asn	Gln	Asp	His	Glu	Lvs	Leu	Phe	Glu	Leu	Ile
25	_		595		•			600			-4		605			
	Leu	Met 610	Glu	Glu	Ile	Arg	Phe 615	Pro	Arg	Thr	Leu	Gly 620	Pro	Glu	Ala	Lys
	Ser		Leu	Ser	Glv	Leu		Lvs	Lvs	Asp	Pro		Gln	Arg	Leu	Glv
	625				- 1	630		-4	-4-		635					640
30		Gly	Ser	Glu	Asp 645	Ala	гла	Glu	Ile	Met 650		His	Arg	Phe	Phe 655	
	Gly	Ile	Val	Trp 660		His	Val	Tyr	Glu 665		Lys	Leu	Ser	Pro 670	-	Phe
	Ive	Pro	GIn		ጥክም	Ser	Glu	Thr		Thr	Δνα	ጥኒፖ	Dhe	Asp	Glu	Glu
35	_,_		675	•				680			**** 3	-1-	685			<b>U</b> _u
00	Dhe	Thr		Gin	Met	Tle	Thr	-	Thr	Dro	Dro	Aen		Asp	Δαη	Ser
		690	71.4	0111	*****		695	220	1111	FIU	FIU	700	OIII	лор	vob	DCI
	Met		Cvs	Val	Asn	Ser		Δνα	Ara	Dro	His		Dro	Gln	Phe	Ser
	705	<b>414</b>	-,-	•	1105	710	014	****9	y	rio	715	2 110	210	0111	1110	720
40		Ser	Δla	Ser	Ser		<b>Δ</b> 1 =				, 13					, 20
40	TAT	Der	A,LG	561		T.11T	WIG									
					725					,						
			(2)	INI	FORM	ATIO	N FO	R SE	Q ID	NO:	140:					
45		1.	() e	יפוזהי	NCE (	ים אנטיי	א הייניים א	DTCm	TOO.							
40		ζ.														
					GTH:				alrs							
					E: ni				_							
					ANDE				Ę							
EΛ			נעו	TOP	OLOG:	I: 1	ınea:	Ľ								
50		,														

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

55

(A) NAME/KEY: Coding Sequence

(B) LOCATION: 1...2391

(D) OTHER INFORMATION:

289

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

		,-	, -								1.0						
5		GAC Asp															48
10		GGC Gly															96
15		TTC Phe															144
.0		AGG Arg 50															192
20		TAC Tyr															240
25		CCT Pro															288
30		GGC Gly	_		_	_											336
35		CAG Gln															384
	_	ATC Ile 130		_													432
40		GAA Glu															480
45		CAG Gln															528
50		GTC Val														_	576
55		CTC Leu														_	624
	GGG	GAT	GAG	ATC	TTC	CTA	CTG	TGT	GAC	AAG	GTG	CAG	AAA	GAG	GAC	ATT	672 2

									•	290								
	Gly	Asp 210	Glu	Ile	Phe	Leu	Leu 215	Сув	Asp	ГАВ	Val	Gln 220	ГÀв	Glu	Asp	Ile		
5										GAG Glu							720	
10										ATT Ile 250							768	
15										GTG Val							816	
10										GAG Glu							864	
20										ATT Ile							912	
25										AAG Lys							960	
30										CGC Arg 330							1008	
35										CCC Pro							1056	
33										GAG Glu					_	_	1104	
40			Gly							GCC Ala			Pro				1152	
45										GCC Ala		Ala				GTA Val 400	1200	
50						Ala										GGC Gly	1248	
r=					Val					Pro					Ala	GGG Gly	1296	
55	GAA	. GGA	ACG	CTG	TCA	GAG	GCC	CTG	CTG	CAG	CTG	CAG	TTI	GAT	' GAT	GAA	1344	290

										291							
	Glu	Gly	Thr 435	Leu	Ser	Glu	Ala	Leu 440	Leu	Gln	Leu	Gln	Phe 445	qaA	qaA	Glu	
5 ·	GAC Asp	CTG Leu 450	GGG	GCC Ala	TTG Leu	CTT Leu	GGC Gly 455	AAC Asn	AGC Ser	ACA Thr	GAC Asp	CCA Pro 460	GCT Ala	GTG Val	TTC Phe	ACA Thr	1392
10	GAC Asp 465	CTG Leu	GCA Ala	TCC Ser	GTC Val	GAC Asp 470	AAC Asn	TCC Ser	GAG Glu	TTT Phe	CAG Gln 475	CAG Gln	CTG Leu	CTG Leu	AAC Asn	CAG Gln 480	1440
15	GGC Gly	ATA Ile	CCT Pro	GTG Val	GCC Ala 485	CCC Pro	CAC His	ACA Thr	ACT Thr	GAG Glu 490	CCC Pro	ATG Met	CTG Leu	ATG Met	GAG Glu 495	TAC Tyr	1488
10	CCT Pro	GAG Glu	GCT Ala	ATA Ile 500	ACT Thr	CGC Arg	CTA Leu	GTG Val	ACA Thr 505	GGG Gly	GCC Ala	CAG Gln	AGG Arg	CCC Pro 510	CCC Pro	GAC Asp	1536
20	CCA Pro	GCT Ala	CCT Pro 515	GCT Ala	CCA Pro	CTG Leu	GGG Gly	GCC Ala 520	CCG Pro	GGG Gly	CTC Leu	CCC Pro	AAT Asn 525	GGC Gly	CTC Leu	CTT Leu	1584
25	TCA Ser	GGA Gly 530	GAT Asp	GAA Glu	GAC Asp	TTC Phe	TCC Ser 535	TCC Ser	ATT Ile	GCG Ala	GAC Asp	ATG Met 540	GAC Asp	TTC Phe	TCA Ser	GCC Ala	1632
30	CTG Leu 545	CTG Leu	AGT Ser	CAG Gln	ATC Ile	AGC Ser 550	TCC Ser	TTG Leu	GAT Asp	CCA Pro	CCG Pro 555	GTC Val	GCC Ala	ACC Thr	ATG Met	GTG Val 560	1680
	AGC Ser	AAG Lys	GGC Gly	GAG Glu	GAG Glu 565	CTG Leu	TTC Phe	ACC Thr	GGG Gly	GTG Val 570	GTG Val	CCC Pro	ATC Ile	CTG Leu	GTC Val 575	GAG Glu	1728
35	CTG Leu	GAC Asp	GGC Gly	GAC Asp 580	GTA Val	AAC Asn	GGC Gly	CAC His	AAG Lys 585	TTC Phe	AGC Ser	GTG Val	TCC Ser	GGC Gly 590	GAG Glu	GGC Gly	1776
40	GAG Glu	GGC Gly	GAT Asp 595	GCC Ala	ACC Thr	TAC Tyr	GGC Gly	AAG Lys 600	CTG Leu	ACC Thr	CTG Leu	AAG Lys	TTC Phe 605	ATC Ile	TGC Cys	ACC Thr	1824
45	ACC Thr	GGC Gly 610	AAG Lys	CTG Leu	CCC Pro	GTG Val	CCC Pro 615	TGG Trp	CCC Pro	ACC Thr	CTC Leu	GTG Val 620	acc Thr	ACC Thr	CTG Leu	ACC Thr	1872
50	TAC Tyr 625	GGC Gly	GTG Val	CAG Gln	TGC Cys	TTC Phe 630	AGC Ser	CGC Arg	TAC Tyr	CCC Pro	GAC Asp 635	CAC His	ATG Met	AAG Lys	CAG Gln	CAC His 640	1920
55		TTC Phe															1968
JJ	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	GTG	AAG	2016 <b>2</b> 9

										292							
	Ile	Phe	Phe	Lys 660	Asp	Asp	Gly	Asn	Tyr 665	-	Thr	Arg	Ala	Glu 670	Val	Lys	
5						CTG Leu											2064
10						AAC Asn											2112
15				_		TAT Tyr 710											2160
				-		ATC Ile											2208
20						CAG Gln											2256
25						CAC His											2304
30						CGC Arg											2352
35						CTC Leu 790								TAA			2394
			(2	) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	141:						
40		(:	(A) (B) (C)	LEN TYP: STR	GTH: E: a ANDE	CHAR 797 mino DNES: Y: 1	ami: aci S: s	no a d ingl	cids								
45	·					TYP: TYPE	-										
		(	xi)	SEQU	ENCE	DES	CRIP	TION	: SE	Q ID	NO:	141:					
50	1	_			5					10					15	Ala Met	
		_		20					25			_		30		Gly	
55	Glu	Arg	35 Ser	Thr	: Asp	Thr	Thr	40 Lys	Thr	His	Pro	Thr	45 : Ile	. Lys	Ile	. Asn	292

		50					55					60				
	Glv		Thr	Glv	Pro	Glv		1/a 1	Δνα	Tla	Cor		17-1	Thr	Lazo	2 000
	65	-7-	****	O±3	1.0	70	1111	Val	ALG	110		пеп	Val	1111	Dys	-
				•			_			_	75		_	_		80
_	Pro	Pro	HIB	Arg		HIS	Pro	HIS	Glu		Val	GIA	Lys	qaA	Cys	Arg
5					85					90					95	
	Asp	Gly	Phe	Tyr	Glu	Ala	Glu	Leu	Cys	Pro	Asp	Arg	Cys	Ile	His	Ser
				100					105					110		
	Phe	Gln	Asn	Leu	Glv	Ile	Gln	Cvs	Val	Lvs	Lvs	Ara	Asp	Leu	Glu	Gln
			115		-			120		-1-	7	5	125			
10	7.7.5	Tla		Gl n	7~~	Tla	GT n		7.05	7	N	D		Gln	777	D
10	A.La		Ser	GIII	ALG	116		1111	ASII	ASII	ASII		РПЕ	GIII	vai	Pro
		130			_		135	_	_	_		140	_			
		GIU	GIU	GIN	Arg		Asp	Tyr	Asp	Leu	Asn	Ala	Val	Arg	Leu	Сув
	145					150					155					160
	Phe	Gln	Val	Thr	Val	Arg	Asp	Pro	Ser	Gly	Arg	Pro	Leu	Arg	Leu	Pro
15					165					170					175	
	Pro	Val	Leu	Pro	His	Pro	Ile	Phe	Asp	Asn	Ara	Ala	Pro	Asn	Thr	Ala
				180					185		5			190		
	Glu.	T.OU	Tare		Circ	N.c.	375.7	Aan		202	C-~	<b>a</b> 1	C	Cys	T 011	<b>61</b>
	ULU	псп		110	Cys	A. 9	Val		ALG	ASII	Ser	GTA		Cys	Leu	GTA
20	~-	_	195			_	_	200	_		<b>-</b>		205		_	
20	GIY		GIU	TTE	Pne	Leu		Cys	Asp	ьуs	val	Gin	Lys	Glu	Asp	He
		210					215					220				
	Glu	Val	Tyr	Phe	Thr	Gly	$\mathtt{Pro}$	Gly	Trp	Glu	Ala	Arg	Gly	Ser	Phe	Ser
	225					230					·235					240
	Gln	Ala	Asp	Val	His	Arq	Gln	Val	Ala	Ile	Val	Phe	Ara	Thr	Pro	Pro
25			-		245	_				250					255	
	ጥህተ	Δla	Agn	Pro		T.en	Gln	Δla	Pro		Δνα	17 = 1	Car	Met		T.011
	-3-	1144	1101	260		204	0.111	nau	265	Vai	n. y	VOI	BCI		GIII	DCu
	<b>3</b>	*	D		3	3	a1	<b>.</b>		<b>~1</b>			<b>~</b> 3 .	270	<b>~</b> 3	
	Arg	Arg		ser	Asp	Arg	GIU		Ser	GIU	Pro	Met		Phe	GIn	ıyr
			275					280					285			
30	Leu	Pro	Asp	Thr	Asp	Asp	Arg	His	Arg	Ile	Glu	Glu	Lys	Arg	Lys	Arg
•		290					295					300				
	Thr	Tyr	Glu	Thr	Phe	Lys	Ser	Ile	Met	Lys	Lys	Ser	Pro	Phe	Ser	Gly
	305					310					315					320
	Pro	Thr	Asp	Pro	Arg	Pro	Pro	Pro	Ara	Ara	Ile	Ala	Val	Pro	Ser	Ara
35					325					330					335	3
	Ser	Ser	λla	Ser		Dro	Tare	Dro	λla		Gln.	Dro	T-1 2-2-	Pro		mb
	501	ber	AT C		VAL	FIU	шуз	FIU		PIU	GIII	PIO	TYL		FITE	TIIL
			_	340			_	_	345			_		350		
	ser	ser		ser	Thr	тте	Asn		Asp	GLu	Phe	Pro	Thr	Met	Val	Phe
			355					360					365			
40	Pro	Ser	Gly	Gln	Ile	Ser	Gln	Ala	Ser	Ala	Leu	Ala	Pro	Ala	Pro	Pro
		370					375					3B0				
	Gln	Val	Leu	Pro	Gln	Ala	Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala	Met	Val
·	385					390					395					400
		Δla	Len	Δla	Gln		Pro	Δla	Dro	Val		Va 1	T.e.11	Ala	Pro	
45					405	2.2.4		7114		410	FIU	VUI	LCu	7.4	415	
70		D	<b>~</b> 1_				_	_			_	_				
	Pro	PTO	GIN		vaı	Ата	Pro	PLO		Pro	гйв	Pro	Thr	Gln	Ala	GIY
	_			420					425					430		
	Glu	Gly	Thr	Leu	Ser	Glu	Ala	Leu	Leu	Gln	Leu	Gln	Phe	Asp	Asp	Glu
			435					440					445			
50	Asp	Leu	Gly	Ala	Leu	Leu	Gly	Asn	Ser	Thr	qaA	Pro	Ala	Val	Phe	Thr
	-	450	•				455				•	460				
	Asp		Ala	Ser	Val	Asp		Ser	Glu	Phe	Gln		Len	Leu	Agn	Gln
	465					470			4	~ ***	475	~~11		4	1	480
		T1~	D	17-1	7.1.		<b>U</b>	mh	mb	<b>~1.</b> -		Wo +	T 01-	Mer	<u>ما</u>	
EE	GTA	116	PLO	٧đ٢		PIO	n1\$	inr	Inr		Pro	met	тел	Met		TAL
55	_	r			485	_				490			_	_	495	_
	Pro	Glu	Ala	Ile	Thr	Arg	Leu	Val	Thr	Gly	Ala	Gln	Arg	Pro	Pro	Asp

				500					505					510				
	Pro	Ala	Pro 515		Pro	Leu	Gly	Ala 520		Gly	Leu	Pro	Asn 525		Leu	Leu		
5	Ser	Gly 530	Asp	Glu	Asp	Phe	Ser 535	Ser	Ile	Ala	Asp	Met 540	Aap	Phe	Ser	Ala		
	Leu 545	Leu	Ser	Gln	Ile	Ser 550	Ser	Leu	Asp	Pro	Pro 555	Val	Ala	Thr	Met	Val 560		
		Lys	Gly	Glu	Glu 565		Phe	Thr	Gly	Val 570		Pro	Ile	Leu	Val 575	Glu		
10	Leu	Asp	Gly	Asp 580		Asn	Gly	His	Lys 585		Ser	Val	Ser	Gly 590		Gly		
	Glu	Gly	Asp 595	_	Thr	Tyr	Gly	Lys		Thr	Leu	Lys	Phe 605		Cys	Thr		
15	Thr	Gly 610		Leu	Pro	Val	Pro 615		Pro	Thr	Leu	Val 620		Thr	Leu	Thr		
,,,	Tyr 625	Gly	Val	Gln	Cys	Phe 630		Arg	Tyr	Pro	Asp 635		Met	Lys	Gln	His 640		
		Phe	Phe	Lys	Ser 645		Met	Pro	Glu	Gly 650		Val	Gln	Glu	Arg 655			
20	Ile	Phe	Phe	Lys 660		Asp	Gly	Asn	Tyr 665		Thr	Arg	Ala	Glu 670	Val	Lys		
	Phe	Glu	Gly 675	Asp	Thr	Leu	Val	Asn 680	Arg	Ile	Glu	Leu	Lys 685	Gly	Ile	Asp		
25	Phe	690	Glu	Asp	Gly	Asn	Ile 695	Leu	Gly	His	Lys	Leu 700	Glu	Tyr	Asn	Tyr		
	Asn 705	Ser	His	Asn	Val	Tyr 710	Ile	Met	Ala	Asp	Lys 715	Gln	Lys	Asn	Gly	Ile 720		
	Lys	Val	Asn	Phe	Lys 725	Ile	Arg	His	Asn	Ile 730	Glu	qaA	Gly	Ser	Val 735	Gln		
30	Leu	Ala	Asp	His 740	Tyr	Gln	Gln	Asn	Thr 745	Pro	Ile	Gly	Asp	Gly 750	Pro	Val		
	Leu	Leu	Pro 755	Asp	Asn	His	Tyr	Leu 760	Ser	Thr	Gln	Ser	Ala 765	Leu	Ser	Lys		
35	Asp	Pro 770	Asn	Glu	Lys	Arg	Asp 775	His	Met	Val	Leu	Leu 780	Glu	Phe	Val	Thr		
	Ala 785	Ala	Gly	Ile	Thr	Leu 790	Gly	Met	Asp	Glu	Leu 795	Tyr	Lys					
			(2	) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	142:							
40		(	-	EQUE														
			(B)	LEN TYP	E: n	ucle	ic a	cid										
45				STR				-	е									
				MOLE FEAT		TYP	E: c	DNA										
50			(B	NA (.)	CATI	ON:	1	2391		ence								
r.r	٠	(	жi)	SEQU	ENCE	DES	CRIP	TION	: SE	Q II	NO:	142:						
55	ATG	GTG	AGC	: AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTO	g ccc	: ATC	CTG	48	294

**295** .

	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu		
5							GTA Val										96	
10							ACC Thr										144	
45		_		_			CCC Pro 55	_				_				_	192	
15							TGC Cys										240	
20							TCC Ser										288	
25							GAC Asp										336	
30							ACC Thr										384	
					_		GGC Gly 135		_								432	
35							GTC Val		_		_			_			480	
40							AAG Lys										528	
45							TAC Tyr										576	
50				Leu			AAC Asn							Ser			624	
			Asp				AAG Lys 215	Arg					Leu			TTC Phe	672	
55	GTG	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	ATG	GAC	GAG	CTG	TAC	AAG	TCC	720	295

	Val 225	Thr	Ala	Ala	Gly	Ile 230	Thr	Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	Lys	Ser 240		
5			AGA Arg														768	
10			CCA Pro														816	
45			CAG Gln 275								-						864	
15			AGC Ser												_		912	
20			ATC Ile														960	
25			GTC Val														1008	
30			AAG Lys														1056	
			TGC Cys 355														1104	
35			GAC Asp		-												1152	
40			TTC Phe														1200	
45			GTG Val														1248	
50					Leu					Pro						TAA Taa	1296	
				Asn					Lys					Asn		AAC Asn	1344	
55	TCT	GGC	. AGC	TGC	CTC	GGT	GGG	GAT	GAG	ATC	TTC	CTA	CTG	TGT	GAC	AAG	1392	296

	Ser	Gly 450	Ser	Cys	Leu	Gly	Gly 455	Asp	Glu	Ile	Phe	Leu 460	Leu	Сув	Asp	Lys	
5	GTG Val 465	CAG Gln	TÀR YYY	GAG Glu	GAC Asp	ATT Ile 470	GAG Glu	GTG Val	TAT Tyr	TTC Phe	ACG Thr 475	GGA Gly	CCA Pro	GGC Gly	TGG Trp	GAG Glu 480	. 1440
10	GCC Ala	CGA Arg	GGC Gly	TCC Ser	TTT Phe 485	TCG Ser	CAA Gln	GCT Ala	GAT Asp	GTG Val 490	CAC His	CGA Arg	CAA Gln	GTG Val	GCC Ala 495	ATT Ile	1488
15	GTG Val	TTC Phe	CGG Arg	ACC Thr 500	CCT Pro	CCC Pro	TAC Tyr	GCA Ala	GAC Asp 505	CCC Pro	AGC Ser	CTG Leu	CAG Gln	GCT Ala 510	CCT Pro	GTG Val	1536
13	CGT Arg	GTC Val	TCC Ser 515	ATG Met	CAG Gln	CTG Leu	CGG Arg	CGG Arg 520	CCT Pro	TCC Ser	GAC Asp	CGG Arg	GAG Glu 525	CTC Leu	AGT Ser	GAG Glu	1584
20	CCC Pro	ATG Met 530	GAA Glu	TTC Phe	CAG Gln	TAC Tyr	CTG Leu 535	CCA Pro	GAT Asp	ACA Thr	GAC Asp	GAT Asp 540	CGT Arg	CAC His	CGG Arg	ATT Ile	1632
25	GAG Glu 545	GAG Glu	AAA Lys	CGT Arg	AAA Lys	AGG Arg 550	ACA Thr	TAT Tyr	GAG Glu	Thr	TTC Phe 555	AAG Lys	AGC Ser	ATC Ile	ATG Met	AAG Lys 560	1680
30	AAG Lys	AGT Ser	CCT Pro	TTC Phe	AGC Ser 565	GGA Gly	CCC Pro	ACC Thr	GAC Asp	CCC Pro 570	CGG Arg	CCT Pro	CCA Pro	CCT Pro	CGA Arg 575	CGC Arg	1728
35	ATT Ile	GCT Ala	GTG Val	CCT Pro 580	TCC Ser	CGC Arg	AGC Ser	TCA Ser	GCT Ala 585	TCT Ser	GTC Val	CCC Pro	AAG Lys	CCA Pro 590	GCA Ala	CCC Pro	1776
35	CAG Gln	CCC Pro	TAT Tyr 595	CCC Pro	TTT Phe	ACG Thr	TCA Ser	TCC Ser 600	CTG Leu	AGC Ser	ACC Thr	ATC Ile	AAC Asn 605	TAT Tyr	GAT Asp	GAG Glu	1824
40 .	TTT Phe	CCC Pro 610	ACC Thr	ATG Met	GTG Val	TTT Phe	CCT Pro 615	TCT Ser	GGG Gly	CAG Gln	ATC Ile	AGC Ser 620	CAG Gln	GCC Ala	TCG Ser	GCC Ala	1872
45	TTG Leu 625	GCC Ala	CCG Pro	GCC Ala	CCT Pro	CCC Pro 630	CAA Gln	GTC Val	CTG Leu	CCC Pro	CAG Gln 635	GCT Ala	CCA Pro	GCC Ala	CCT Pro	GCC Ala 640	1920
50		GCT Ala															1968
	CCA Pro	GTC Val	CTA Leu	GCC Ala 660	CCA Pro	GGC Gly	CCT Pro	CCT Pro	CAG Gln 665	GCT Ala	GTG Val	GCC Ala	CCA Pro	CCT Pro 670	GCC Ala	CCC Pro	2016
55	AAG	ccc	ACC	CAG	GCT	GGG	GAA	GGA	ACG	CTG	TCA	GAG	GCC	CTG ·	CTG	CAG	2064 2

										230							
• .	Lys	Pro	Thr 675	Gln	Ala	Gly	Glu	Gly 680	Thr	Leu	Ser	Glu	Ala 685	Leu	Leu	Gln	
5 .		CAG Gln 690															2112
10	GAC Asp 705	CCA Pro															2160
45		CAG Gln									Ala						2208
15		ATG Met															2256
20		CAG Gln															2304
25		CCC Pro 770															2352
30		ATG Met												TAA			2394
			(2)	INI	FORM	ATIOI	N FOI	R SE	Q ID	NO:	143;						
35		Ė)	(A) (B) (C)	EQUENCE TYP) STRI	STH: E: an ANDEI	797 mino ONES	amin acio	no ao i ingle	cids			٠					
40			ii) r	OLE RAGMI	COLE	TYPI	E: p	rote:									
4E		(၁	xi) 8	SEQUI	ENCE	DES	CRIP'	rion	: SE	Q ID	NO:	143:					
45	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile 15	Leu	
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly	
50	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile	
	_	Thr 50		-	-		55			-		60					
55	65	Thr	_	_		70	_			_	75		_			80 Lys	

					85					90					95	
				100	Phe				105					110		
, 5			115		Gly			120					125		_	-
		130			Glu		135					140				
	145				His	150					155					160
10	•				Asn 165					170					175	
				180	Asp				185					190	_	_
15			195		Pro	_		200	_				205			
		210			Asn		215		_			220				
20	225				Gly	230					235					240
20					Arg 245			_		250					255	
				260	Gln			_	265	_				270		•
25			275		Gly			280					285			
		290			Pro		295					300				
00	305				Ile	310					315	_				320
30					Lys 325					330					335	
				340	Сув				345					350		
35			355		His			360			_		365			_
		370			Glu		375					380				
	385				Val	390					395	_				400
40					Leu 405	_				410					415	
				420	Leu				425					430		
45			435		Thr			440			_		445			
		450			Leu		455					460				
	465				Asp	470			_		475	_				480
50					Phe 485				•	490					495	
				500	Pro		_		505					510		
55			515		Gln			520		•			525			
	Pro	met	GIU	rne	Gln	TYY	Leu	Pro	ASD	Inr	ASP	ASP	Arg	អាវន	arg	TTE

		530					535					540				
	Glu 545	Glu	Lys	Arg	Lys	Arg 550	Thr	Tyr	Glu	Thr	Phe 555	ŗà	Ser	Ile	Met	Lys 560
5	ГÀЗ	Ser	Pro	Phe	Ser 565	Gly	Pro	Thr	Asp	Pro 570	Arg	Pro	Pro	Pro	Arg 575	Arg
	Ile	Ala	Val	Pro 580	Ser	Arg	Ser	Ser	Ala 585	Ser	Val	Pro	Lys	Pro 590	Ala	Pro
	Gln	Pro	Tyr 595	Pro	Phe	Thr	Ser	Ser 600	Leu	Ser	Thr	Ile	Asn 605	Tyr	qaA	Glu
10	Phe	Pro 610	Thr	Met	Val	Phe	Pro 615	Ser	Gly	Gln	Ile	Ser 620	Gln	Ala	Ser	Ala
	Leu 625	Ala	Pro	Ala	Pro	Pro 630	Gln	Val	Leu	Pro	Gln 635	Ala	Pro	Ala	Pro	Ala 640
15	Pro	Ala	Pro	Ala	Met 645	Val	Ser	Ala	Leu	Ala 650	Gln	Ala	Pro	Ala	Pro 655	Val
	Pro	Val	Leu	Ala 660	Pro	Gly	Pro	Pro	Gln 665	Ala	Val	Ala	Pro	Pro 670	Ala	Pro
	ГÀа	Pro	Thr 675	Gln	Ala	Gly	Glu	Gly 680	Thr	Leu	Ser	Glu	Ala 685	Leu	Leu	Gln
20	Leu	Gln 690	Phe	Asp	Asp	Glu	Asp 695	Leu	Gly	Ala	Leu	Leu 700	Gly	Asn	Ser	Thr
	Asp 705	Pro	Ala	Val	Phe	Thr 710	Asp	Leu	Ala	Ser	Val 715	Asp	Asn	Ser	Glu	Phe 720
25	Gln	Gln	Leu	Leu	Asn 725	Gln	Gly	Ile	Pro	Val 730	Ala	Pro	His	Thr	Thr 735	Glu
	Pro	Met	Leu	Met 740	Glu	Tyr	Pro	Glu	Ala 745	Ile	Thr	Arg	Leu	Val 750	Thr	Gly
	Ala	Gln	Arg 755	Pro	Pro	Asp	Pro	Ala 760	Pro	Ala	Pro	Leu	Gly 765	Ala	Pro	Gly
30	Leu	Pro 770	Asn	Gly	Leu	Leu	Ser 775	Gly	Ąsp	Glu	Asp	Phe 780	Ser	Ser	Ile	Ala
	Asp 785	Met	Asp	Phe	Ser	Ala 790	Leu	Leu	Ser	Gln	Ile 795	Ser	Ser			

## CLAIMS

5

10

15

20

- 1. A method for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on a mechanically intact living cell or mechanically intact living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cell or cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, the association resulting in a modulation of the luminescence characteristics of the luminophore, and processing the recorded variation in the spatially distributed light to provide quantitative information correlating the spatial distribution to the degree of the influence on the cellular response.
- 2. A method according to claim 1, as used for extracting quantitative information relating to an influence on an intracellular pathway involving redistribution of at least one component associated with the pathway, or part thereof, the method comprising recording the result of the influence on mechanically intact living cell or cells, as manifested in spatially distributed light emitted from a luminophore which is present in the cell or cells and which is capable of being redistributed, by modulation of the pathway, in a manner which is related to the redistribution of the at least one component of the intracellular pathway, processing the recorded result to provide quantitative information about the spatially distributed light and correlating the quantitative information to the degree of the influence on the intracellular pathway.
  - 3. A method according to claim 1 or 2, wherein the quantitative information which is indicative of the degree of the cellular response to the influence or the result of the influence on the intracellular pathway is extracted from the recording or recordings according to a predetermined calibration based on responses or results, recorded in the same manner, to known degrees of a relevant specific influence.
- 4. A method according to any of the preceding claims, wherein the influence is contact between the mechanically intact living cell or the group of mechanically intact living cells with a

chemical substance and/or incubation of the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance.

- 5. A method according to claim 4 wherein the substance is a substance whose effect on an intracellular pathway is to be determined.
  - 6. A method according to any of the preceding claims, wherein the recording is made at a single point in time after the application of the influence.
- 7. A method according to any of claims 1-5, wherein the recording is made at two points in time, one point being before, and the other point being after the application of the influence.
  - 8. A method according to any of claims 1-5, wherein the recording is performed at a series of points in time, in which the application of the influence occurs at some time after the first time point in the series of recordings, the recording being performed, e.g., with a predetermined time spacing of from 0.1 seconds to 1 hour, preferably from 1 to 60 seconds, more preferably from 1 to 30 seconds, in particular from 1 to 10 seconds, over a time span of from 1 second to 12 hours, such as from 10 seconds to 12 hours, e.g., from 10 seconds to one hour, such as from 60 seconds to 30 minutes or 20 minutes.

20

- 9. A method according to any of claims 1-7, wherein the cell or cells is/are fixed at a point in time after the application of the influence at which the response has been predetermined to be significant, and the recording is made at an arbitrary later time.
- 25 10. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence.

- 11. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of associating with a component which is capable of being redistributed in manner which is physiologically relevant to the degree of the influence.
- 12. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed in a manner which is experimentally determined to be correlated to the degree of the influence.
- 13. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed, by modulation of the intracellular pathway, in substantially the same manner as the at least one component of the intracellular pathway.
- 14. A method according to any of claims 1-13, wherein the luminophore is a luminophore which is capable of being quenched upon spatial association with a component which is redistributed by modulation of the pathway, the quenching being measured as a decrease in the intensity of the luminescence.
- 15. A method according to any of claims 1-13, wherein the variation or result with respect to the spatially distributed light emitted by the luminophore is detected by a change in the resonance energy transfer between the luminophore and another luminescent entity capable of delivering energy to the luminophore, each of which has been selected or engineered to become part of, bound to or associated with particular components of the intracellular pathway, and one of which undergoes redistribution in response to the influence, thereby changing the amount of resonance energy transfer, the change in the resonance energy transfer being measured as a change in the intensity of emission from the luminophore.
  - 16. A method according to claim 15, wherein the change in the intensity of the emission from the luminophore is sensed by a single channel photodetector which responds only to the average intensity of the luminophore in a non-spatially resolved fashion

17. A method according to any of claims 1-16, wherein the property of the light being recorded is intensity, fluorescence lifetime, polarization, wavelength shift, or other property which is modulated as a result of the underlying cellular response.

5

- 18. A method according to any of claims 1-15 or 17, wherein the recording of the spatially distributed light is performed using a recording system which records the spatial distribution of a recordable property of the light in the form of an ordered array of values.
- 19. A method according to claim 18, wherein the recording of the spatial distribution of the recordable property of the light is performed using a charge transfer device such as a CCD array or a vacuum tube device such as a vidicon tube.
- 20. A method according to any of the preceding claims, wherein the light to be measured
   passes through a filter which selects the desired component of the light to be measured and rejects other components.
  - 21. A method according to any of the preceding claims, wherein the recording of the spatial distribution of the recordable property of light is performed by fluorescence microscopy.

20

- 22. A method according to any of the preceding claims, wherein the recording of the variation or result with respect to light emitted from the luminophore is performed by recording the spatially distributed light as one or more digital images, and the processing of the recorded variation to reduce it to one or more numbers representative of the degree of redistribution comprises a digital image processing procedure or combination of digital image processing procedures.
- 23. A method according to any of claims 2-22, wherein the intracellular pathway is an intracellular signalling pathway.

- 24. A method according to any of the preceding claims, wherein the luminophore is a fluorophore.
- 25. A method according to any of the preceding claims wherein the luminophore is a polypeptide encoded by and expressed from a nucleotide sequence harboured in the cell or cells.
- 26. A method according to any of the preceding claims, wherein the luminophore is a hybrid polypeptide comprising a fusion of at least a portion of each of two polypeptides one of which comprises a luminescent polypeptide and the other one of which comprises a biologically active polypeptide, as defined herein.
- 27. A method according to claim 26, wherein the luminescent polypeptide is a GFP as defined herein.
  - 28. A method according to claim 27 wherein the GFP is selected from the group consisting of green fluorescent proteins having the F64L mutation as defined herein.
- 29. A method according to claim 28 wherein the GFP is a GFP variant selected from the group consisting of F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP.
  - 30. A method according to any of the previous claims for detecting intracellular translocation of a biologically active polypeptide affecting intracellular processes upon activation, the method comprising
    - a) culturing one or more cells containing a nucleotide sequence coding for a hybrid polypeptide comprising a GFP which is N- or C-terminally tagged, optionally through a linker, to a biologically active polypeptide under conditions permitting expression of the nucleotide sequence,

- b) modulating the activity of the biologically active polypeptide by incubating the cell or cells with a substance having biological activity and
- c) measuring the fluorescence produced by the incubated cell or cells and determining the result or variation with respect to the fluorescence, such result or variation being indicative of the translocation of a biologically active polypeptide in said cell.
- 31. A method according to claim 30, wherein the nucleotide sequence is a DNA sequence.
- 32. A method according to claim 30 or 31, wherein the modulation is an activation.

15

25

- 33. A method according to claim 30 or 31, wherein the modulation is a deactivation.
- 34. A method according to any of claims 30-33 wherein the fluorescence of the cell or cells is measured prior to the modulation, and the result or variation determined in step (c) is a change in fluorescence compared to the fluorescence measured prior to the modulation.
- 35. A method according to any of claims 30-34, wherein the intracellular processes are intracellular signalling pathways.
- 36. A method according to claim 34, wherein the change in fluorescence measured in step (c) comprises determining a change in the spatial distribution of the fluorescence.
  - 37. A method according to any of the preceding claims wherein the mechanically intact living cell or cells is/are a mammalian cell/mammalian cells which, during the time perold over which the influence is observed, is/are incubated at a temperature of 30°C or above, preferably at a temperature of from 32°C to 39°C, more preferably at a temperature of from 35°C to 38°C, and most preferably at a temperature of about 37°C.

- 38. A method according to any of the preceding claims, wherein the at least one mechanically intact living cell is part of a matrix of identical or non-identical cells.
- 39. A method according to any of claims 1-36 and 38, wherein the cell or cells is/are selected from the group consisting of fungal cells, such as a yeast cell; invertebrate cells including insect cells; and vertebrate cells, such as mammalian cells.
  - 40. A nucleic acid construct coding for a fusion polypeptide comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and a GFP, with the proviso that the construct is not a construct coding for a fusion polypeptide in which the biologically active polypeptide is selected from the group consisting of PKC-alpha, PKC-gamma, and PKC-epsilon.
- 41. A nucleic acid construct coding for a fusion polypeptide comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and an F64L mutant of GFP.
  - 42. A nucleic acid construct according to claim 40 or 41, wherein the biologically active polypeptide is a protein kinase or a phosphatase.

- 43. A nucleic acid construct according to any of claims 40-42 wherein the GFP is N- or C-terminally tagged, optionally via a peptide linker, to the biologically active polypeptide or part thereof.
- 44. A nucleic acid construct according to any of claims 40, 41 and 43, wherein the biologically active polypeptide is a transcription factor or a part thereof which changes cellular localisation upon activation.

- 45. A nucleic acid construct according to any of claims 40, 41 and 43, wherein the biologically active polypeptide is a protein, or a part thereof, which is associated with the cytoskeletal network and which changes cellular localisation upon activation.
- 46. A nucleic acid construct according to any of claims 40-43, wherein the biologically active polypeptide is a protein kinase or a part thereof which changes cellular localisation upon activation.
- 47. A nucleic acid construct according to claim 46, wherein the protein kinase is a ser ine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
  - 48. A nucleic acid construct according to claim 46, wherein the protein kinase is a tyrosine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
  - 49. A nucleic acid construct according to claim 46, wherein the protein kinase is a phospholipid-dependent serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
- 50. A nucleic acid construct according to claim 46, wherein the protein kinase is a cAMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 51. A nucleic acid construct according to claim 50 which codes for a PKAc-F64L-S65T-GFP fusion.
  - 52. A nucleic acid construct according to claim 46, wherein the protein kinase is a cGMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.

53. A nucleic acid construct according to claim 46, wherein the protein kinase is a calmodulin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

- 54. A nucleic acid construct according to claim 46, wherein the protein kinase is a mitogenactivated serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 55. A nucleic acid construct according to claim 54, which codes for an ERK1-F64L-S65T-GFP fusion.
  - 56. A nucleic acid construct according to claim 54, which codes for an EGFP-ERK1 fusion.
- 57. A nucleic acid construct according to claim 46, wherein the protein kinase is a cyclindependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 58. A nucleic acid construct according to claim 42 or 43, wherein the biologically active polypeptide is a protein phosphatase or a part thereof capable of changing cellular localisation upon activation.
  - A nucleic acid construct according to any of claims 40-58 which is a DNA construct.
- 60. A nucleic acid construct according to any of claims 40-59 wherein the gene encoding GFP is derived from Aequorea victoria.
  - 61. A nucleic acid construct according to claim 60 in which the gene encoding GFP is the gene encoding EGFP as defined herein.

62. A nucleic acid construct according to claim 60 in which the gene encoding a GFP is a gene encoding a GFP variant selected from F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP.

5

10

- 63. A DNA construct according to claim 59 and 61 or, where applicable, 62, which is a construct as identified by any of the DNA sequences shown in SEQ ID NO: 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, and 142, or is a variant thereof capable of encoding the same fusion polypeptide or a fusion polypeptide which is biologically equivalent thereto, as defined herein.
- 64. A cell containing a nucleic acid construct according to any of claims 40-63 and capable of expressing the sequence encoded by the construct.

- 65. A cell according to claim 64, which is a eukaryotic cell.
- 66. A cell according to claim 64, which is selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells, including insect cells, and vertebrate cells, such as mammalian cells.
  - 67. A cell according to claim 66, which is a mammalian cell.
- 68. An organism carrying in at least one of its component cells a nucleic acid sequence as contained in the constructs according to any of claims 40-59, said cell being capable of expressing said nucleic acid sequence.
  - 69. An organism according to claim 68 which is selected from the group consisting of unicellular and multicellular organisms, such as a mammal.

- 70. A fluorescent probe comprising a GFP which is N- or C-terminally tagged, optionally via a peptide linker, to a biologically active polypeptide or a part or a subunit thereof which is a component of a intracellular signalling pathway as defined herein, the probe being a probe which is encoded by the nucleic acid construct according to any of claims 40-59.
- 71. A method according to any of claims 1-39, wherein the luminophore is a fusion polypeptide as encoded by the nucleic acid construct according to any of claims 40-63.
- 72. A method according to any of claims 1-39 or 71 in which the method of the invention is used in a screening program as defined herein.
  - 73. An apparatus for measuring the distribution of fluorescence in at least one cell, and thereby any change in the distribution of fluorescence in at least one cell, which includes the following component parts: (a) a light source, (b) a means for selecting the wavelength(s) of light from the source which will excite the fluorescence of the protein, (c) a means for rapidly blocking or pass ing the excitation light into the rest of the system, (d) a series of optical elements for conveying the excitation light to the specimen, collecting the emitted fluorescence in a spatially resolved fashion, and forming an image from this fluorescence, (e) a bench or stand which holds the container of the cells being measured in a predetermined geometry with respect to the series of optical elements, (f) a detector to record the spatially resolved fluorescence in the form of an image, (g) a computer or electronic system and associated software to acquire and store the recorded images, and to compute the degree of redistribution from the recorded images.

25

15

- 74. An apparatus according to claim 73 in which some or all of the system is automated.
- 75. An apparatus according to claim 73 in which components d and e comprise a fluorescence microscope.

- 76. An apparatus according to claim 73 in which component f is a CCD camera.
- 77. An apparatus according to claim 73 in which the image is formed and recorded by an optical scanning system.

5

- 78. An apparatus according to claim 73 in which a liquid addition system is used to add a known or unknown compound to any or all of the cells in the cell holder at a time determined in advance.
- 79. An apparatus according to claim 78 in which the liquid addition system is under the control of the computer or electronic system.
  - 80. A method according to any of claims 1-79 wherein the method is a screening program for the identification of a biologically active substance as defined herein that directly or indirectly affects an intracellular signalling pathway and is potentially useful as a medicament, wherein the result of the individual measurement of each substance being screened which indicates its potential biological activity is based on measurement of the redistribution of spatially resolved luminescence in living cells and which undergoes a change in distribution upon activation of an intracellular signalling pathway.

20

25

30

15

- 81 A method according to any of claims 1-79 wherein the method is a screening program for the identification of a biologically toxic substance as defined herein that exerts its toxic effect by interfering with an intracellular signalling pathway, wherein the result of the individual measurement of each substance being screened which indicates its potential biologically toxic activity is based on measurement of the redistribution of said fluorescent probe in living cells and which undergoes a change in distribution upon activation of an intracellular signalling pathway.
- 82. A method according to any of claims 1-80 wherein a fluorescent probe is used in backtracking of signal transduction pathways as defined herein.

5

15

20

- 83. A method of treating a condition or disease related to the intracellular function of a protein kinase comprising administering to a patient suffering from said condition or disease an effective amount of a compound which has been discovered by any method according to the invention.
- 84. A compound that modulates a component of an intracellular pathway as defined herein, as determined by a method according to the method of the invention.
- 85. A medical composition comprising a therapeutic amount of a compound identified according the method of the invention.
  - 86. A method of selectively treating a patient suffering from an ailment which responds to medical treatment comprising obtaining a primary cell or cells from said patient, transfecting the cell or cells with at least one DNA sequence encoding a fluorescent probe according to the invention, culturing the cell or cells under conditions permitting the expression of said probes and exposing it to an array of medicaments suspected of being capable of alleviating said ailment, then comparing changes in fluorescence patterns or redistribution patterns of the fluorescent probes in the intact living cell or cells to detect the cellular response to the specific medicaments (obtaining a cellular action profile), then selecting a medicament(s) based on desired activity and acceptable level of side effects and administering an effective amount of said medicament(s) to said patient.
- 87. A method according to any of claims 1-80 of identifying a drug target among the group of biologically active polypeptides which are components of intracellular signalling pathways.

WO 98/45704 PCT/DK98/00145

Fig 1

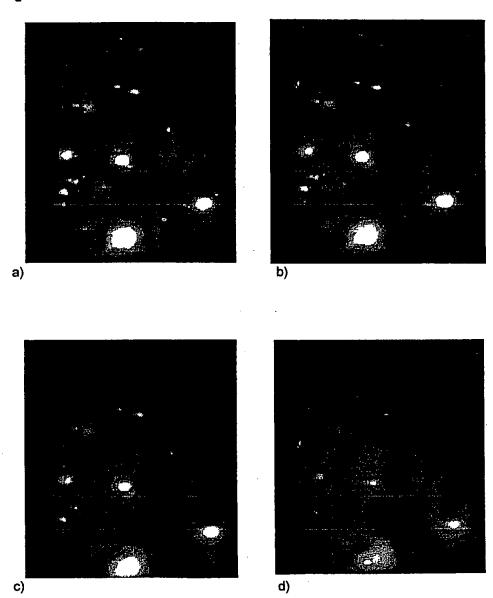


Fig 2

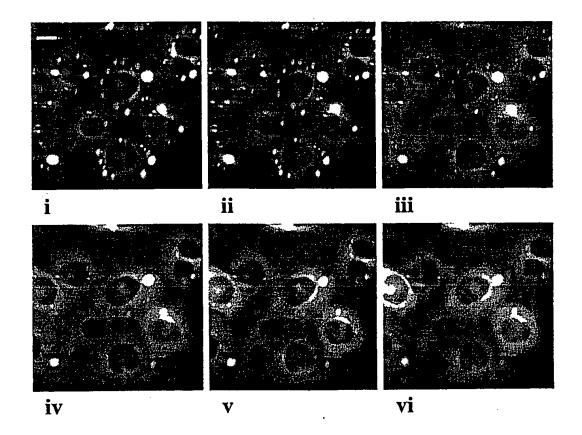
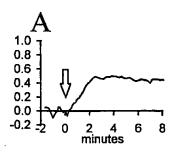
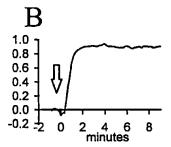
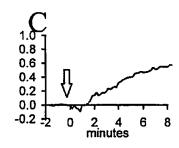
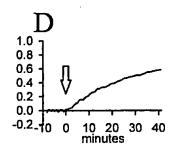


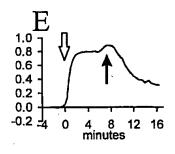
Fig 3

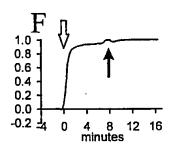


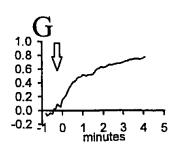












1.

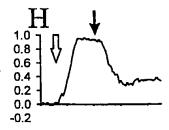


Fig 4

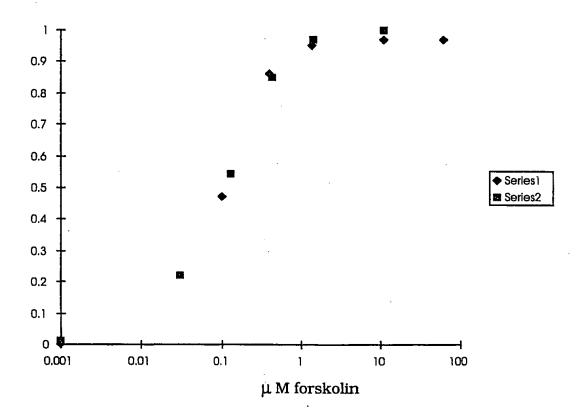


Fig 5

[forskolin]µM	t <sub>1/2max</sub> / s	t <sub>max</sub> /s
1	115±21	310±31
10	69±14	224±47
50	47±10	125±28

Fig 6

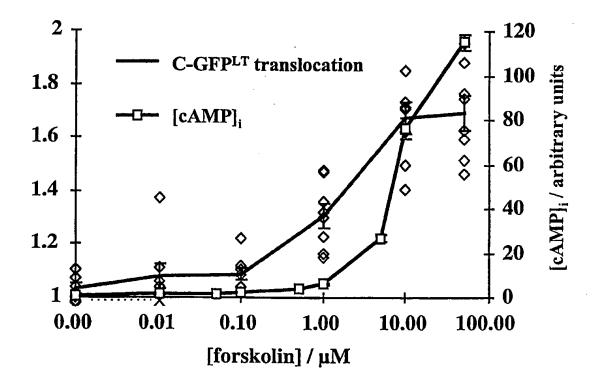
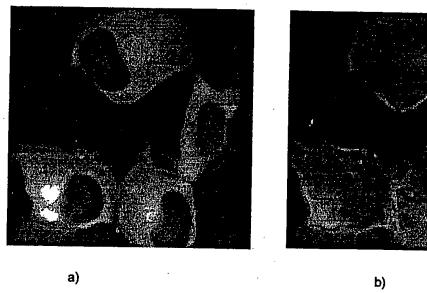
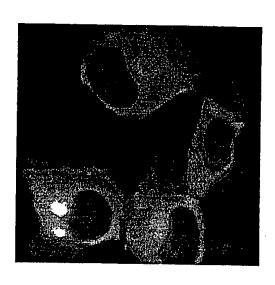


Fig 7

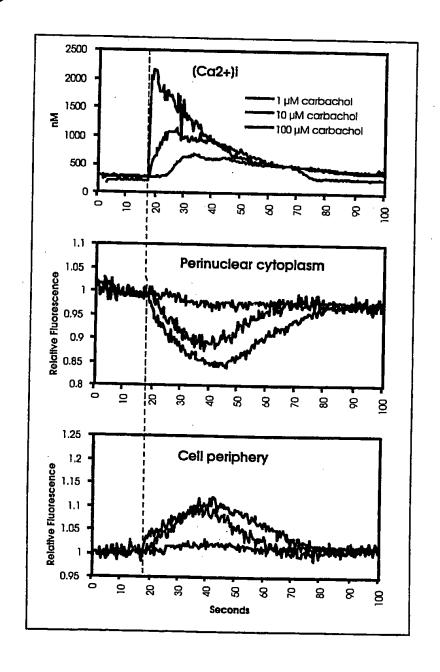


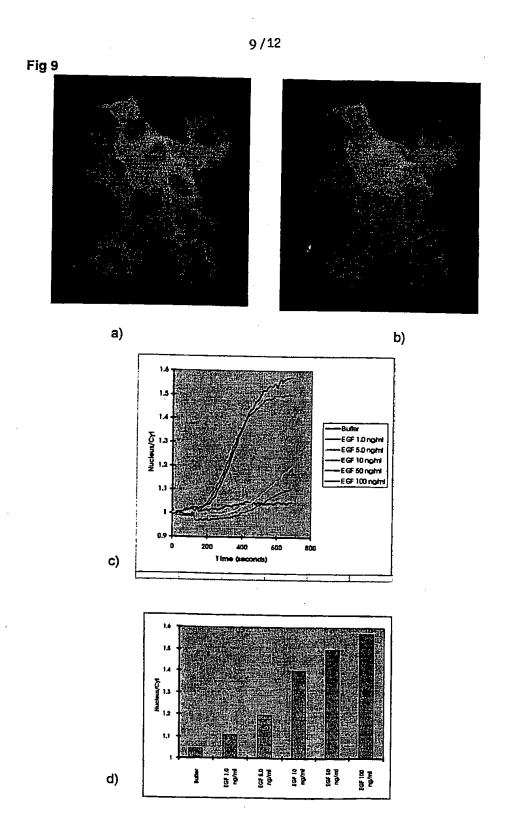


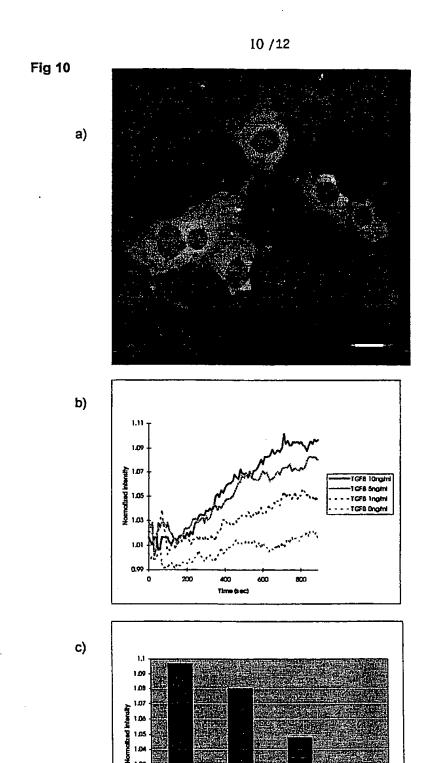


c)

Fig 8







TGF8 5ng/ml

TGF8 Ong/ml

1.01

TGF8 10ng/mt

Fig 11



Fig. 12

